

SUMMARY OF CHANGES

Protective Effect of Quadrivalent Vaccine in Young HIV-positive Males who have Sex with Males (Version 5.0)

NCI Protocol #: AMC-072

Local Protocol #: AMC-072

NCI Version Date: 05/02/2014

Update Date: 05/02/2014

#	Section	Change Description
1.	<i>Cover Page</i>	<u>Changed from:</u> Version 4.0 NCI Version Date: January 31, 2012 <u>Changed to:</u> Version 5.0 NCI Version Date: May 2, 2014 Update Date: May 2, 2014
2.	<i>Footer</i>	<u>Changed from:</u> AMC # 072 (Version 4.0) 01/31/2012 NCI Version Date 01/31/2012 <u>Changed to:</u> AMC # 072 (Version 5.0) 05/02/2014 NCI Version Date 05/02/2014
3.	<i>Global</i>	<u>Changed from:</u> AdEERS <u>Changed to:</u> References to the “Adverse Event Expedited Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.
4.	<i>Abbreviations</i>	<u>Changed from:</u> Intravenous immunoglobulin <u>Changed to:</u> Intravenous immunoglobulin

#	Section	Change Description
5.	2.2.1	<p><u>Changed from:</u></p> <p>To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing penile/scrotal condyloma and HPV-6, -11, -16, -18- associated perinal/anal disease in HIV-positive males who have sex with males (MSM) age 13-26 years by comparing the incidence of these lesions among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline..</p> <p><u>Changed to:</u></p> <p>To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing penile/scrotal condyloma and HPV-6, -11, -16, -18- associated perianal/anal disease in HIV-positive males who have sex with males (MSM) age 13-26 years by comparing the incidence of these lesions among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline.</p>
6.	3.1.2	<p><u>Changed from:</u></p> <p>HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests.</p> <p><u>Changed to:</u></p> <p>HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests. If the participant's HIV status is documented by an outside physician, the protocol team strongly recommends obtaining a copy of the HIV laboratory reports from this physician. All confirmatory tests and the physician's note must be on file before the participant is enrolled. In the rare circumstance where only an outside physician's note with no supporting laboratory documentation is available, the local site should have additional tests performed to verify the participant's HIV status. One of the following additional tests should be performed:</p> <ul style="list-style-type: none"> ▪ A rapid HIV test ▪ ELISA and Western blot ▪ Chemiluminescence immunoassay and Western blot ▪ HIV RNA > 2000 copies/mL ▪ HIV antigen test
7.	3.2.3	<p><u>Changed from:</u></p> <p>HGAIN (e.g., AIN 2 or 3, or perianal intraepithelial neoplasia grade 2 or 3), or invasive carcinoma at pre-entry on biopsy.</p> <p><u>Changed to:</u></p> <p>HGAIN (e.g., AIN 2 or 3, or perianal intraepithelial neoplasia grade 2 or 3) or invasive carcinoma at pre-entry on biopsy, or participant has a history of invasive carcinoma or any prior anal cytology result of HSIL or ASC-H.</p>

#	Section	Change Description
8.	5.2.1	<p><u>Changed from:</u></p> <p>Text added</p> <p><u>Changed to:</u></p> <p>The ACSR tissue biopsy may be collected at week 104 even if a baseline ACSR tissue biopsy donation was not collected. The ACSR tissue biopsy may only be collected with the participant's consent, if there are suspected lesions observed during HRA (i.e., not from normal areas), and must be a separate specimen from the diagnostic biopsy.</p>
9.	5.3.1	<p><u>Changed from:</u></p> <p>HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests.</p> <p><u>Changed to:</u></p> <p>HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests. If the participant's HIV status is documented by an outside physician, the protocol team strongly recommends obtaining a copy of the HIV laboratory reports from this physician. All confirmatory tests and the physician's note must be on file before the participant is enrolled. In the rare circumstance where only an outside physician's note with no supporting laboratory documentation is available, the local site should have additional tests performed to verify the participant's HIV status. One of the following additional tests should be performed:</p> <ul style="list-style-type: none"> ▪ A rapid HIV test ▪ ELISA and Western blot ▪ Chemiluminescence immunoassay and Western blot ▪ HIV RNA > 2000 copies/mL ▪ HIV antigen test
10.	4.3.2	<p><u>Changed from:</u></p> <p>The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (DARF) (available on the CTEP home page (http://ctep.cancer.gov) or by calling the Pharmaceutical Management Branch at 301-496-5725) or a site-specific form that captures the same elements as the NCI DARF.</p> <p><u>Changed to:</u></p> <p>The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (DARF) (available on the CTEP home page (http://ctep.cancer.gov) or by calling the Pharmaceutical Management Branch at 240-276-6575) or a site-specific form that captures the same elements as the NCI DARF.</p>

#	Section	Change Description
11.	5.3.7	<p><u>Changed from:</u></p> <p>The penis, scrotum and perianal area will be examined for signs of HPV-related lesions. The presence or absence of penile/scrotal/perianal condyloma will be recorded on the CRFs. Anal cytology and HRA with biopsy of visible disease will be performed to assess anal HPV-associated disease. Sampling of the penis/scrotum, perianal area and the anal canal for HPV DNA and other sexually transmitted agents will be performed.</p> <p><u>Changed to:</u></p> <p>The penis, scrotum and perianal area will be examined for signs of HPV-related lesions. The presence or absence of penile/scrotal/perianal condyloma will be recorded on the CRFs. Anal cytology and HRA with biopsy of visible disease will be performed to assess anal HPV-associated disease. Sampling of the penis/scrotum, perianal area and the anal canal for HPV DNA and other sexually transmitted agents will be performed. HRA and anal cytology are required assessments at baseline and Weeks 28, 52, 78, and 104. Only visual inspection of the penis, scrotum, and perianal area are required at Week 8 and Week 24.</p>
12.	5.3.7	<p><u>Changed from:</u></p> <p>Record all diagnoses identified by the CTCAE criteria (see Section 7.0 for details) for clinical events and other diseases. Furthermore, any diagnosis of a cellulitis, abscess or other infection at the vaccination site should be recorded.</p> <p><u>Changed to:</u></p> <p>Record all diagnoses identified by the CTCAE Version 4.0 criteria (see Section 7.0 for details) for clinical events and other diseases. Furthermore, any diagnosis of a cellulitis, abscess or other infection at the vaccination site should be recorded.</p>
13.	5.3.9	<p><u>Changed from:</u></p> <p>Immunologic Studies</p> <p>To document eligibility for those subjects who are not on antiretroviral therapy, CD4+ level must be equal or greater than ≥ 350 cells/mm³ within 90 days of study entry from a laboratory that possesses a CLIA certification or equivalent. CD4+/CD8+ will be obtained from all subjects within 90 days of study entry and at Week 28.</p> <p><u>Changed to:</u></p> <p>Immunologic Studies</p> <p>To document eligibility for those subjects who are not on antiretroviral therapy, CD4+ level must be equal or greater than ≥ 350 cells/mm³ within 90 days prior to study entry from a laboratory that possesses a CLIA certification or equivalent. CD4+/CD8+ will be obtained from all subjects within 90 days prior to study entry and at Week 28.</p>
14.	5.3.10	<p><u>Changed from:</u></p> <p>Plasma HIV-1 RNA</p> <p>On-study plasma HIV-1 RNAs will be done in real time. Plasma HIV viral load will be obtained within 90 days of study entry and at Week 28.</p> <p><u>Changed to:</u></p> <p>Plasma HIV-1 RNA</p> <p>On-study plasma HIV-1 RNAs will be done in real time. Plasma HIV viral load will be</p>

#	Section	Change Description
		obtained within 90 days prior to study entry and at Week 28.
15.	7.3.1	<p><u>Changed from:</u></p> <p>In the rare occurrence when internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to the AMC Operations Center at 240-238-2842. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into CTEP-AERS by the original submitter at the site.</p> <p><u>Changed to:</u></p> <p>A 24-hour notification is to be made to the AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into CTEP-AERS by the original submitter at the site.</p>
16.	7.3.1	<p><u>Changed from:</u></p> <p>Expedited Reporting Timelines for Investigational Agents</p> <p><u>Changed to:</u></p> <p>Expedited Reporting Timelines for Adverse Events that occur within 8 Weeks¹ of the Last Dose of the Investigational Agent on Phase 2 and 3 Studies</p> <p><i>The title of this table was revised to add the appropriate reference to footnote 1 for the legacy expedited AE reporting table.</i></p>
17.	7.3.2	<p><u>Changed from:</u></p> <p>All AE reports submitted through AdEERS will be forwarded to designated Merck personnel by the AMC Operations Center.</p> <p><u>Changed to:</u></p> <p>All SAE reports submitted through CTEP-AERS that are at least possibly attributed to study vaccine administration will be forwarded to designated Merck personnel by the AMC Operations Center.</p>
18.	8.1	<p><u>Changed from:</u></p> <p>If we assume hypothetically that the incidence of persistent HPV infection w/o vaccine is 10 per 100 PY and the the expected incidence of HPV-associated disease is 5 per 100 PY, then the attached table shows the effect size and associated lower rate of infection that can be detected with the anticipated numbers of patients for a “per protocol” population for each HPV type.</p> <p><u>Changed to:</u></p> <p>If we assume hypothetically that the incidence of persistent HPV infection w/o vaccine is 10 per 100 PY and the expected incidence of HPV-associated disease is 5 per 100 PY, then the attached table shows the effect size and associated lower rate of infection that can be detected with the anticipated numbers of patients for a “per protocol” population for each HPV type.</p>

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19.	Appendix I	<p><u>Changed from:</u></p> <p>Footnote added (Clinical assessments at Week 8 and 24).</p> <p><u>Changed to:</u></p> <p>2 HRA and anal cytology are not required assessments at Week 8 and Week 24. Visual inspection of the penis, scrotum, and perianal area should be done at Week 8 and Week 24.</p>
20.	Appendix I	<p><u>Changed from/to:</u></p> <p>Footnote reference for HRA at baseline changed from footnote 2 to footnote 4.</p>
21.	Appendix I	<p><u>Changed from:</u></p> <p>Text moved</p> <p><u>Changed to:</u></p> <p>Moved the following required procedures: Swab for anal HPV DNA PCR, swab for penile/scrotal HPV PCR, serum HPV antibody testing, urine testing for GC/Chlamydia, oral HPV PCR testing and exam from column Screening/Pre-Entry to column Entry Injection 1.</p>
22.	Appendix I Footnote 5	<p><u>Changed from:</u></p> <p>Footnote reference for anal biopsy changed from footnote 4 to footnote 5.</p> <p><u>Changed to:</u></p> <p>Anal biopsies (if lesion suspected).</p>
23.	Appendix I	<p><u>Changed from:</u></p> <p>ACSR Donation (Optional if patient consents)</p> <p><u>Changed to:</u></p> <p>The ACSR donation is now listed in two rows, one for each sample type: ACSR Biopsy Donation (Optional if patient consents) and ACSR Blood Donation (Optional if patient consents). Within both rows, the optional ACSR donation schedule was moved from the column for Entry/Visit 1 to the column Screening/Pre-Entry. The donation remains scheduled for Week 104 for both specimen types.</p> <p>Added footnote 6 to the row for ACSR Biopsy Donation:</p> <p>6 Anal biopsies for ACSR donation may be obtained with the subject's consent from suspected lesions. The tissue biopsy for ACSR donation must be separate from the diagnostic biopsy.</p>
24.	Appendix V	<p><u>Changed from:</u></p> <p>All cytological specimens should be processed and examined locally. Cytological slides from subjects who enter the trial should be available for central review upon request.</p> <p><u>Changed to:</u></p> <p>All cytological specimens should be processed and examined locally. If insufficient or inadequate cytology results are obtained, the cytology assessment should be repeated if possible. Cytological slides from subjects who enter the trial should be available for</p>

#	Section	Change Description
		central review upon request.
25.	Appendix VI	<p><u>Changed from:</u></p> <p><i>Text added</i></p> <p><u>Changed to:</u></p> <p><u>High resolution anoscopy is performed at screening and weeks 28, 52, 78 and 104. Biopsies are obtained if a lesion is suspected. One of the study outcomes is any incident AIN or anal/perianal condyloma associated with HPV 16, 18, 6 or 11 DNA as determined by PCR analysis of the anal tissue biopsy. Biopsies are fixed in formalin and sent to the local pathology lab for interpretation. We are requesting that the cassettes containing the biopsy be sent to the Palefsky lab. After the procedures described below are performed, the Palefsky lab will ship the remaining specimens back to the pathology lab that sent them.</u></p> <p><u>Specimens may be shipped to the Palefsky lab quarterly and will be returned to the pathology lab within 1 month.</u></p>
26.	Appendix VI Sample labeling	<p><u>Changed from:</u></p> <p>Specimen Type: “Penile/Scrotal Swab”, “Perianal Swab” or “Anal Swab”</p> <p><u>Changed to:</u></p> <p><u>Specimen Type: “Penile/Scrotal Swab”, “Perianal Swab” or “Anal Swab” or “Anal biopsy”</u></p>
27.	Appendix VII	<p><u>Changed from:</u></p> <p>Biopsy any areas clinically suspicious for AIN.</p> <p><u>Changed to:</u></p> <p><u>Biopsy area if a lesion is suspected.</u></p>
28.	Appendix VII	<p><u>Changed from:</u></p> <p>Biopsies will be processed and read locally at the institution.</p> <p>The tissue block, along with a copy of the surgical pathology report should be available for central review upon request. If the block is not available, a representative H & E stained section and six unstained slides should be submitted. All materials will be retained unless return is specifically requested. Tissue will be evaluated for histology as demonstrated by H & E staining.</p> <p><u>Changed to:</u></p> <p><u>Biopsies will be processed and read locally at the institution.</u></p> <p><u>The tissue block, along with a copy of the surgical pathology report should be available for central review upon request. If the block is not available, a representative H & E stained section and six stained slides should be submitted. All materials will be retained unless return is specifically requested. Tissue will be evaluated for histology as demonstrated by H & E staining.</u></p> <p><u>All slides should be sent to the following address for central pathology review:</u></p> <p><u>Teresa M. Darragh, MD</u></p>

#	Section	Change Description
		<p>UCSF/Mt. Zion Medical Center Dept. of Pathology, Box 1785 1600 Divisadero Street, Room B217 San Francisco, CA 94115 Tel: 415-353-7861 Fax: 415-353-7676</p> <p>Slides from UCSF that are read by local pathologist Dr. Teresa Darragh will be reviewed by Dr. Mieke van Zante for central review.</p> <p>When affixing the specimen label, do not wrap the label around the slide as any protrusion at the bottom will result in the slide not sitting flat on the microscope stage. In addition, do not cover the slide's accession number. In some cases, the label may need to be trimmed to allow the barcode and 9-digit portion of the label to be affixed at the top of the slide.)</p> <p>Shipping Instructions</p> <ol style="list-style-type: none"> 1. Place the labeled slides into a specimen container or a slide box if available. Place the container or slide box in bubble wrap or other adequate cushioning. Use sturdy outer packaging to prevent breakage. 2. Affix the FED-EX airbill on blank side of the shipper. 3. Mark "OTHER" in the airbill under "Packaging". 4. Under airbill section "special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED". 5. Enter FED-EX account #: [REDACTED] 6. Place "From/To" information onto areas provided on the shipper. Specimens are accepted MONDAY through THURSDAY only. All specimens should be shipped by FedEx 2-day service to Dr. Darragh at the address listed above: 7. Make certain that shipper is visibly labeled "Exempt human specimen." 8. RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS. 9. Place the box in the FedEx pickup area at your site or call to request a package pickup. <p>Record of Specimens</p> <p>This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimens.</p>
29.	<i>Appendix IX</i>	<p><u>Changed from:</u></p> <p>Serum shipments to Merck (PPD) should be sent routinely on the first Monday or Tuesday of the month (or as requested by the Clinical team) to the following address:</p> <p><u>Changed to:</u></p> <p>Serum shipments to Merck (PPD) should be sent <u>quarterly</u> on the first Monday or Tuesday of the month (or as requested by the Clinical team) to the following address:</p>
30.	<i>Appendix X</i>	<p><u>Changed from:</u></p> <p>AMC DATA SAFETY AND MONITORING PLAN</p> <p>(Version 4.0 • September 13, 2010)</p> <p><u>Changed to:</u></p>

#	Section	Change Description
		AMC DATA SAFETY AND MONITORING PLAN (Version 5.0 • January 28, 2014) <i>Revisions to Version 5.0 of the DSMP are limited to the CTEP-AERS change described in Item #3.</i>
31.	Appendix XII	<u>Changed from:</u> 1) How often do you currently smoke cigarettes? (Choose one) <input type="checkbox"/> Not at all (skip to question 4) <input type="checkbox"/> Some days <input type="checkbox"/> Every day <input type="checkbox"/> I prefer not to answer (skip to question #3) <u>Changed to:</u> 1) How often do you currently smoke cigarettes? (Choose one) <input checked="" type="checkbox"/> Not at all (skip to question #3) <input type="checkbox"/> Some days <input type="checkbox"/> Every day <input type="checkbox"/> I prefer not to answer (skip to question #3)



AIDS MALIGNANCY CLINICAL TRIALS CONSORTIUM

AMC PROTOCOL #072: Protective Effect of Quadrivalent Vaccine in Young HIV-positive Males who have Sex with Males

A Multi-Center Trial of the AIDS Malignancy
Clinical Trials Consortium (AMC) and the Adolescent Medicine
Trials Network (ATN) **for HIV/AIDS Interventions**

Sponsored by: National Cancer Institute
Office of HIV AIDS and Malignancy (OHAM)
and
The Eunice Kennedy Shriver National Institutes of
Child Health and Human Development Pediatric,
Adolescent and Maternal AIDS Branch

**Pharmaceutical Support
and Vaccine Provided by:** Merck & Co., Inc.

Study Vaccine: Quadrivalent Human Papillomavirus (Types 6, 11,
16 and 18) Recombinant Vaccine, NSC 745201

Protocol Chair: Joel Palefsky, MD

Protocol Co-chairs: Bret Rudy, MD
Jessica Kahn MD, MPH

Version 5.0, May 2, 2014
NCI Version Date May 2, 2014

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: Protective Effect of quadrivalent vaccine in young HIV-positive males who have sex with males **(Version 5.0, 05/02/2014)**, as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the above protocol may be made without written permission from the Protocol Chair(s).

Signature

Date (mm/dd/yyyy)

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ACSR	AIDS Cancer Specimen Resource
ACTG	AIDS Clinical Trials Group
CTEP-AERS	Adverse Event Expedited Reporting System
AdvantageEDC SM	AMC Internet Data Entry System
AE	Adverse Event
AIN	Anal intraepithelial neoplasia
ALT	Alanine transaminase
AMC	AIDS Malignancy Consortium Clinical Trials
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ASC-H	Atypical squamous cells suggestive of HSIL
ASCUS	Atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATN	Adolescent Medicine Trials Network
BUN	Blood urea nitrogen
CDC	Centers for Disease Control
CDUS	Clinical Data Update System
CIN	Cervical intraepithelial neoplasia
CLIA	Clinical Laboratory Improvement Act
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Event reporting
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
DARF	Drug Accountability Record Form
DSMC	Data Safety and Monitoring Committee
EC	AIDS Malignancy Consortium Executive Committee

EGL	External genital lesions
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration
HAART	Highly-active antiretroviral therapy
HERS	HIV Epidemiology Research Study
HGAIN	High-grade anal intraepithelial neoplasia
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRA	High Resolution Anoscopy
HSIL	High-grade intraepithelial lesion(s)
IATA	International Air Transport Association
IDB	Investigational Drug Branch
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional review board
IVIG	Intravenous immunoglobulin
LSIL	Low grade intraepithelial lesion(s)
LSM	Lymphocyte Separation Medium
mcg	Microgram
mg	Milligram
ml	Milliliter
MSM	Males who have sex with males
NCI	National Cancer Institute
NICHD	National Institute of Child Health and Human Development
OHAM	Office of HIV and AIDS Malignancy
OHRP	Office for Human Research Protections
PCR	Polymerase chain reaction
PIO	Protocol Information Office
RNA	Ribonucleic acid

SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STI	Sexually transmitted infection
VAERS	Vaccine Adverse Event Reporting System
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-like particles

SITES PARTICIPATING IN THE STUDY

This protocol will be open to all interested AMC and ATN sites approved by the AMC HPV Working Group. The approval will be based on the capacity to perform high resolution anoscopy (HRA).

PROTOCOL ROSTER

AMC #072

Protective Effect of quadrivalent vaccine in young HIV-positive males who have sex with males

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AMC Website for ATN Sites:

<https://web.emmes.com/study/amc/atn/atn.htm>

SCHEMA

AMC-072: Protective Effect of Quadrivalent Vaccine in Young HIV-positive Males who have Sex with Males

DESIGN:	Open-label, phase 2, single-arm study
DURATION:	2 years
SAMPLE SIZE:	150
POPULATION:	HIV-positive males who have sex with males 13 to 26 years of age without AIN
REGIMEN:	All participants will be vaccinated with the Quadrivalent Human Papillomavirus Recombinant vaccine (0.5 mL Gardasil®) by intramuscular injection at Day 1, Weeks 8 and 24.
PRIMARY OBJECTIVES:	<ol style="list-style-type: none">1) To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing penile/scrotal condyloma and HPV-6, -11, -16, -18- associated perianal/anal disease in HIV-positive males who have sex with males (MSM) age 13-26 years by comparing the incidence of these lesions among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline.2) To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing persistent anogenital infection with HPV-6, -11, -16, or 18 in HIV-positive MSM age 13-26 years by comparing the incidence of persistent infection among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline.3) To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing anogenital lesions associated with HPV 6,-11,-16, -18 and persistent infection with these types, in HIV-positive MSM age 13-26 years by comparing the incidence of lesions and persistent infection among those naïve to the relevant types at baseline to incident lesions and infection among MSM naïve to these HPV types who participated in the Merck 020 protocol and who received placebo as part of the protocol.

- SECONDARY OBJECTIVES:**
- 1) To define the safety of the HPV-6, -11, -16, -18 vaccine in HIV-positive MSM age 13-26 years
 - 2) To evaluate the levels and persistence of HPV 6, 11, 16 and 18 Ab titers after the vaccination series among subjects who are seropositive and seronegative for those HPV types at baseline.
 - 3) To examine whether the protective effect and antibody titers vary as a function of the following at the time of initial vaccination: Subject age, HAART treatment status, HIV viral load, CD4 + T cell count, nadir CD4 level.
- TERTIARY OBJECTIVES:**
- 1) To quantify anogenital HPV DNA viral load prior to and after receipt of the quadrivalent HPV vaccine.
 - 2) To identify and quantify HPV types in the oral cavity of HIV-positive MSM prior to and after receipt of the quadrivalent HPV vaccine.
 - 3) To identify HPV strain variants among HIV-positive participants prior to and after receipt of the quadrivalent HPV vaccine.
 - 4) Assess the prevalence and incidence of urinary gonorrhea and Chlamydia trachomatis infection at baseline and their relationship with prevalent and incident anogenital HPV infection and anal condyloma or AIN.
 - 5) To characterize young men's risk perceptions, sexual behaviors, and STI diagnosis after HPV vaccination.

1.0 BACKGROUND AND RATIONALE

1.1 Background

Human papillomavirus (HPV) is a DNA virus of which over 100 types have been identified. Approximately 30 types are sexually transmitted and infect the anogenital area of both men and women.⁽¹⁾ The lifetime risk for anogenital HPV infection among sexually active men and women is at least 50%.⁽²⁾

Anal HPV, AIN and anal carcinoma

Anal carcinoma is strongly related to infection with high-risk types of HPV, as has been seen for cervical, vaginal, vulvar, and penile cancer.⁽³⁾ The incidence of anal cancer in men who have sex with men is estimated to be 35 cases/100,000 person-years.⁽⁴⁾ This incidence is comparable to that observed for cervical cancer before the introduction of routine Papanicolaou screening. The rate of anal cancer is estimated to be twice as high in HIV-positive as in HIV-negative men who have sex with men.⁽⁵⁾ Several studies suggest that the incidence of anal cancer in HIV-positive men who have sex with men has increased in the era of highly-active antiretroviral therapy (HAART).^(6,7)

Similar to cervical cancer, anal cancer is preceded by high-grade anal intraepithelial neoplasia (HGIN). AIN is readily detected by anal cytology, and abnormal cytological results should prompt high resolution anoscopy and biopsy of areas suspicious for AIN. Areas of HGIN can be treated with ablative therapy in an attempt to reduce the incidence of invasive cancer. The prevalence of cytological abnormalities among HIV-1-infected MSM has been estimated at 65%, and the prevalence of high-risk HPV at 78%.⁽⁸⁾ Approximately 30% are positive by HPV DNA PCR for type 16, 20% for type 18, and 10% for both (Wilkin, personal communication). The majority of HIV-1-infected MSM have multiple types of high-risk HPV detected by PCR. Among HIV-positive women, the prevalence of anal cytological abnormalities has been estimated at 26%, and the prevalence of HPV at 76%.⁽⁹⁾

Response to recombinant protein vaccines in HIV-positive populations

As the availability of potent antiretroviral regimens has increased the life expectancy and quality of life of HIV-positive patients, vaccinations for preventable infections have increased significance. Poor responses to standard vaccination series have been documented in HIV-positive patients.⁽¹⁰⁻¹⁴⁾ Meta-analysis of eight studies designed to evaluate the efficacy of hepatitis A vaccination in HIV-positive patients using the standard vaccination series revealed a low response rate.⁽¹³⁾ The overall response rate for HIV-positive patients was 64% in a combined total of 458 subjects. Individual studies have yielded a lower proportion of patients achieving adequate hepatitis A antibody titers. In a small retrospective analysis, the hepatitis A vaccination response rate was only 48% compared with reported rates of 100% in HIV-negative patients.⁽¹⁵⁾

Compared with success rates of greater than 90% in immunocompetent hosts, HIV-positive patients respond to hepatitis B vaccination at rates of 17.5% – 56%^(11, 14, 16, 17) Strategies to improve the vaccination response rate include increasing the amount of the dose, the use of a four-dose schedule, and the administration of booster vaccinations.^(18, 19) In the HIV population, there is evidence to suggest that an adequate antibody response may not be sustained over time as expected. The use of a six-dose strategy that produced initial antibody

titers comparable to the immunocompetent population found that adequate hepatitis B antibody was maintained for only 59% of subjects one year after completion of the modified series.⁽²⁰⁾

Investigators have analyzed patient-specific predictors associated with responders to both hepatitis A and B vaccination. The presence of low-level viremia has been consistently associated with failure to respond to hepatitis vaccination. In a logistic regression model, Overton, et al. showed that only HIV RNA level below 400 copies/mL at the time of hepatitis B vaccination was associated with a protective antibody response, while CD4+ count at time of vaccination was not found to be statistically significant.⁽¹⁷⁾ In HIV-positive children, an undetectable plasma HIV-1 RNA and CD4+ T-cell percent greater than 20% predicted response to hepatitis A vaccination.⁽²¹⁾ Nadir CD4+ count has not been shown to predict the development of protective antibody in HIV patients for either hepatitis A or B vaccination in any study to date.

Gardasil®

Gardasil® (Merck & Co., Inc.) was approved by the FDA in June 2006 and is indicated in girls and women 9-26 years of age for the prevention of cervical cancer, genital warts, and genital precancerous or dysplastic lesions caused by human papillomavirus (HPV) types 6, 11, 16, and 18. Gardasil protects recipients against 4 types of HPV, including the two types that cause most cervical cancers and the two types that cause most genital warts. It consists of virus-like particles generated by the expression of the major capsid protein L1 from HPV types 6, 11, 16, and 18 with an aluminum adjuvant. This vaccine targeting HPV types 6, 11, 16, and 18 can substantially reduce the acquisition of infection and clinical disease caused by these types. The ACIP recommends that Gardasil be routinely given to girls when they are 11 or 12 years of age, before people become sexually active (i.e., before women are exposed to the viruses). Gardasil can be administered as early as age 9 years, and can also be given to women 13 to 26 years old. Gardasil is to be given as a three dose series completed over 6 months.

For many viruses, an infection induces neutralizing antibodies that are a correlate of immune protection. HPV cannot be cultivated in tissue culture and true neutralization assays are not commercially available. Instead, capsid proteins of HPV produced in non-mammalian cells self-assemble into virus-like particles (VLP) and can be used as reagents in enzyme immunoassays.⁽²²⁾ These VLP-based immunoassays and the scales for these assays are highly type-specific and thus, comparison across types and to other assays are not possible. (See [Appendix III, Merck Gardasil Product Information](#)).

Natural HPV infection induces a low level of antibody production that for most types does not seem to confer complete protection against subsequent type-specific HPV infection. Furthermore, it has not been possible to establish minimum antibody levels that protect against clinical disease. Viscidi, et al. evaluated the prevalence of serum antibodies to HPV types 16, 18, 31, 35, and 45 in 829 HIV-positive and 413 HIV-negative risk-matched women enrolled in HERS and analyzed the association of seropositivity with risk of detection of HPV DNA in the genital tract during follow up. The seroprevalence of HPV 16 antibodies was 51.8% in HIV-positive women compared with 45.5% in HIV-negative women, and that of HPV 18 was 52.0% and 35.6% in HIV-positive and -negative women respectively.⁽²³⁾ There was no statistically significant difference in the risk of a new infection with the

homologous HPV type between HPV-seropositive and HPV seronegative women.⁽²³⁾ This suggests that natural HPV infection does not confer complete immunoprotection for most HPV types.

Almost all HIV-negative girls and women who received the Gardasil vaccine became HPV 6, 11, 16, and 18 seropositive one month after the third vaccine dose (99.8%, 99.8%, 99.8%, and 99.5% respectively). The titers peaked at month 7 and stabilized through month 36 at levels above baseline. The aim of this study is to evaluate whether the new quadrivalent HPV vaccine induces detectable serum titers against the HPV types included in the vaccine among HIV-positive adult men and to establish its safety in this population.

Immunogenicity and efficacy results for quadrivalent HPV vaccine in girls and women

Immunogenicity results of Protocol 007 showed that administration of a 3-dose regimen (0, 2, 6 Months) of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20 mcg (Gardasil) generates robust anti-HPV 6, 11, 16, and 18 responses 4 weeks after the completion of the vaccination regimen and durable anti-HPV 6, 11, 16, and 18 responses 2.5 years following completion of the vaccination regimen. Efficacy results of Protocol 007 showed that administration of a 3-dose regimen of Gardasil substantially reduced the risk for acquisition of persistent HPV 6-, 11-, 16-, or 18-related infection or HPV 6-, 11-, 16-, or 18-related genital disease and substantially reduced the risk for development of a composite endpoint of HPV 6-, 11-, 16- or 18-related CIN or EGL.

Immunogenicity results of the Protocol 016 adult/adolescent substudy showed that for each of the 4 HPV types, the vaccine induced numerically higher HPV 6, 11, 16, 18 geometric mean titers (GMTs) 4 weeks Postdose 2 (Month 3) and 4 weeks Postdose 3 (Month 7) in 10- to 15-year-old male and female subjects than in 16- to 23-year-old female subjects. Immunogenicity results of the Protocol 016 end expiry substudy showed that lower dose formulations of Gardasil induced anti-HPV responses at Month 7 that were statistically non-inferior to those generated following administration of a 3-dose regimen.

Immunogenicity results from Protocols 013 and 015 have been consistent with Protocols 007 and 016 and have demonstrated ongoing vaccine immunogenicity for at least 24 Months post-vaccination that has correlated with demonstrable vaccine efficacy.

In clinical trials, administration of a 3-dose regimen of Gardasil to women naïve to the relevant vaccine HPV types, at Day 1 and the through the completion of the vaccination regimen, was over 90% efficacious in preventing the development of:

- HPV 16- and 18-related CIN 2/3 and adenocarcinoma in situ (obligate cervical cancer precursors);
- HPV 16- and 18-related vulvar intraepithelial neoplasia (VIN) 2/3 and vaginal intraepithelial neoplasia (VaIN) 2/3 (obligate precursors to HPV-related vulvar and vaginal cancer, respectively);
- HPV 6- and 11-related external genital lesions (including condyloma acuminata);
- HPV 6-, 11-, 16-, and 18-related CIN; and
- HPV 6-, 11-, 16-, and 18-related persistent infection

Efficacy studies of Gardasil in young HIV-negative men

The FDA recently extended the approval of Gardasil for use in males ages 9 to 26 for the prevention of anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. However, data on the efficacy of Gardasil in young HIV-positive men is limited. In bridging studies the antibody response in adolescent boys appears similar to that of adolescent girls. In a recent clinical trial of Gardasil in HIV-negative boys and men aged 16-26 (Merck 020), unpublished data show that among those naïve to vaccine-specific HPV types, the vaccine was effective to prevent development of external genital condyloma acuminatum with an efficacy of 90%, and protection against persistent external genital infection with HPV 6, 11, 16 and 18 ranged from 79% to 96%. Nearly 100% of boys and men seroconverted and the vaccine was well tolerated.

Safety and tolerability results for quadrivalent HPV vaccine in women

In clinical studies of GARDASIL™ about 25,900 people received at least one shot of GARDASIL™. About 2000 people received at least one shot of a similar vaccine at higher or lower doses than GARDASIL™. Fourteen studies are still ongoing. In these studies, GARDASIL™ has been generally well tolerated. Among the reported serious vaccine-related side effects:

Eight (8) people had serious side effects judged by the study doctor to be related to GARDASIL™.

- Wheezing and shortness of breath (1 subject)
- Upset stomach with vomiting or diarrhea (1 subject)
- Disease of the large bowel (called ulcerative colitis) starting 389 days after the third dose (1 subject)
- Muscular weakness (1 subject)
- Facial paralysis (1 subject)
- Pain and joint stiffness (limiting movement) at the place where the study vaccine was injected (1 subject)
- Vaginal bleeding that lasted on and off for up to 2 ½ months after each of two study vaccinations (1 subject)
- Severe headache with high blood pressure on the day of a study vaccination that lasted 5 days and 1 day, respectively (1 subject)

Common side effects occur in 1 or more out of 100 subjects. The side effects judged to be related to study vaccine or placebo and seen more commonly among subjects who received GARDASIL™ than subjects who received placebo include:

- Fever
- Nausea
- Dizziness
- Headache
- Pain in extremity (pain in arm or leg)

See section 4.1.3 for a comprehensive list of adverse events (AEs) or refer to the FDA-approved package insert available at www.gardasil.com.

Safety and immunogenicity of the quadrivalent HPV vaccine in HIV-positive males and females

A few studies have been performed of the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-positive males and females. The PACTG P1047 study has reported preliminary data indicating that the vaccine is well tolerated in adolescent HIV-positive boys and girls, with high HPV seroconversion rates, although the titers to HPV 6 and were lower than historical HIV-negative controls. The vaccine has also been shown to be well-tolerated among HIV-positive MSM in AMC-052.

1.2 Rationale

The men most likely to benefit from this vaccine are those who are seronegative to HPV 6, 11, 16 and 18, and who do not have those types detected by HPV DNA PCR. In addition, men who are seropositive to those types and PCR negative may benefit by “boosting” the humoral response to those types and preventing re-infection. Prior studies in HIV-positive women suggest that the humoral response associated with natural infection was not protective against re-infection. There are few data on the seroprevalence to HPV types 6, 11, 16, and 18 in HIV-positive MSM; none of which used the Merck assay. A study of 59 HIV-positive MSM found that 36% and 27% were seropositive for types 16 and 18, respectively.⁽²⁴⁾ A second study of 154 HIV-positive MSM found that 42% were seropositive for type 16.⁽²⁵⁾ In the AMC 052 study of HIV-positive MSM, most of whom were over the age of 30 years, at baseline, 29% were positive for HPV 16 antibodies, 19% were positive for HPV 18 antibodies, 38% were positive for HPV 6 antibodies and 30% were positive for HPV 11 antibodies. Among HIV-positive women, approximately 50% were seropositive to type 16 and 50% to type 18. Anal infection with high-risk HPV is extremely common among HIV-positive MSM older than 20 years of age with a prevalence of 80%.

Not surprisingly, the prevalence of anal HPV infection and disease was lower among younger HIV-positive MSM. In one study of young HIV-positive MSM, (Moscicki AB AIDS. 2003;17:311-20), 14% had anal HPV 16, none had HPV 18 DNA and 23% had HPV 6 and/or HPV11.

Although the quadrivalent vaccine appears to be immunogenic and well tolerated in HIV-positive individuals, no studies have been done yet on the protective effect of the vaccine in these populations regardless of their age. The vaccine has been shown to be highly efficacious in HIV-negative populations to date, but the efficacy is restricted to those who are sero- or DNA-negative to a given HPV type. Efficacy studies in HIV-positive individuals are hampered by the high prevalence of prior exposure to vaccine HPV types, and an efficacy study among HIV-positive individuals would be best performed in a HIV-positive population with relatively limited prior exposure to HPV, but with a high risk of incident infection and disease within the period of the study. The optimal study population to determine the protective effect of the vaccine among HIV-positive individuals is young (age 13-26) HIV-positive MSM, and this group is the focus of the present study. This study will evaluate the protective effect of developing type 16-, 18- 6- or 11-associated AIN or anal condyloma, as well as persistent infection with these types. Because the quadrivalent HPV vaccine was recently approved for use in boys by the FDA, a placebo control arm is not practical. Therefore in this study, all participants will be vaccinated, and the incidence of HPV infection and disease will be compared between those with and without exposure to HPV at

baseline prior to vaccination.

1.3 Study Design

A Phase II open-label, single arm study of the safety and immunogenicity of HPV vaccination directed against types 6, 11, 16 and 18 in HIV-positive MSM aged 13 to 26 years. Individuals will be screened with a liquid-based anal cytology and HPV DNA PCR. Eligible subjects must have no history of anal cancer or high-grade anal intraepithelial neoplasia. Subjects are excluded if they have an anal cytology showing high-grade squamous intraepithelial lesion(s) (HSIL), atypical squamous cells cannot rule out HSIL (ASC-H) or cytology suggestive of carcinoma. At study entry, subjects will give samples for HPV DNA PCR, and HPV type-specific serologies. Subjects will receive the HPV vaccine on Day 1, Week 8 and Week 24. Subsequently, subjects will be seen for study visits through 24 months after entry (18 months after vaccination). HPV DNA PCR, liquid based anal cytology, high resolution anoscopy with biopsy and HPV serologies (types 6, 11, 16 and 18) will be obtained during study follow-up.

Safety will be assessed by the occurrence of grade 3 or 4 events (Section 7.0). Routine liver function tests and chemistries will be obtained at screening and at Week 28, 4 weeks after completion of the vaccination series. Plasma HIV-1 RNA, CD4 cell count will be obtained at Baseline (study entry) and at Week 28. The immunogenicity will be assessed by comparing antibody titers to the four types at screening, 7 months, 12, 18 and 24 months post-vaccination.

2.0 HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

The protective effect of the HPV -6, -11, -16, -18 vaccine in preventing anogenital disease associated with vaccine types will be significantly higher in HPV-seronegative and DNA-negative HIV-positive MSM age 13 to 26 years vs. men who have evidence of prior exposure to vaccine HPV types, i.e. who are HPV-seropositive and/or DNA-positive for those types.

2.2 Primary Objectives

- 2.2.1 To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing penile/scrotal condyloma and HPV-6, -11, -16, -18- associated perianal/anal disease in HIV-positive males who have sex with males (MSM) age 13-26 years by comparing the incidence of these lesions among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline.
- 2.2.2 To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing persistent anogenital infection with HPV-6, -11, -16, or 18 in HIV-positive MSM age 13-26 years by comparing the incidence of persistent infection among those naïve to the relevant HPV type(s) at baseline to those who are not naïve at baseline..
- 2.2.3 To determine the protective effect of the HPV-6, -11, -16, -18 vaccine in preventing anogenital lesions associated with HPV 6,-11,-16, -18 and persistent infection with these types, in HIV-positive MSM age 13-26 years by comparing the incidence of lesions and persistent infection among those naïve to the relevant types at baseline to incident lesions and infection among MSM naïve to these HPV types who participated in the Merck 020 protocol and who received placebo as part of the protocol.

2.3 Secondary Objectives

- 2.3.1 To define the safety of the HPV-6, -11, -16, -18 vaccine in HIV-positive MSM age 13-26 years.
- 2.3.2 To evaluate the levels and persistence of HPV 6, 11, 16 and 18 Ab titers after the vaccination series among subjects who are seropositive and seronegative at baseline.
- 2.3.3 To examine whether the protective effect and antibody titers vary as a function of the following at the time of initial vaccination: Subject age, HAART treatment status, HIV viral load, CD4 + T cell count, nadir CD4 level.

2.4 Tertiary Objectives

- 2.4.1 To quantify anogenital HPV DNA viral load prior to and after receipt of the quadrivalent HPV vaccine.
- 2.4.2 To identify and quantify HPV types in the oral cavity of HIV-positive MSM prior to and after receipt of the quadrivalent HPV vaccine.

- 2.4.3 To identify HPV strain variants among HIV-positive participants prior to and after receipt of the quadrivalent HPV vaccine.
- 2.4.4 Assess the prevalence and incidence of urinary gonorrhea and Chlamydia trachomatis infection at baseline and their relationship with prevalent and incident anogenital HPV infection and anal condyloma or AIN.
- 2.4.5 To characterize young men's risk perceptions, sexual behaviors, and STI diagnosis after HPV vaccination.

3.0 SUBJECT SELECTION

3.1 Inclusion Criteria

- 3.1.1 Men age 13 to 26 years with a history of at least one male sexual partner. “Men” is defined as those documented “male” at birth (including male-to-female transgendered persons).
- 3.1.2 HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests. If the participant’s HIV status is documented by an outside physician, the protocol team strongly recommends obtaining a copy of the HIV laboratory reports from this physician. All confirmatory tests and the physician’s note must be on file before the participant is enrolled. In the rare circumstance where only an outside physician’s note with no supporting laboratory documentation is available, the local site should have additional tests performed to verify the participant’s HIV status. One of the following additional tests should be performed:
 - A rapid HIV test
 - ELISA and Western blot
 - Chemiluminescence immunoassay and Western blot
 - HIV RNA > 2000 copies/mL
 - HIV antigen test
- 3.1.3 If receiving antiretroviral therapy:
 - Receipt of antiretroviral therapy for at least 3 months prior to entry
 - No change in antiretroviral therapy within 30 days prior to entry
- 3.1.4 If not receiving antiretroviral therapy:
 - CD4 cell count ≥ 350 cells/mm³ within 90 days prior to study entry
 - No plans to start antiretroviral therapy prior to Week 28
- 3.1.5 Normal anal cytological result, LSIL/condyloma or ASCUS result within 90 days prior to entry, and no HGAIN on biopsy.
- 3.1.6 Absolute neutrophil count (ANC) > 750 cells/mm³; hemoglobin ≥ 9.0 g/dL; platelet count $\geq 100,000$ /mm³; AST (SGOT), ALT (SGPT) $\leq 3 \times$ ULN; Total or conjugated (direct) bilirubin $\leq 2.5 \times$ ULN within 45 days prior to entry, with the exception of isolated hyperbilirubinemia that is considered due to atazanavir.
- 3.1.7 Calculated creatinine clearance ≥ 60 mL/min (Cockcroft-Gault Formula).
- 3.1.8 Karnofsky performance score ≥ 70 within 45 days prior to entry (See [Appendix II.](#))

3.2 Exclusion Criteria

- 3.2.1 Current or history of anal or peri-anal carcinoma
- 3.2.2 Anal cytological result of HSIL, atypical squamous cells suggestive of HSIL (ASC-

H), or suggestive of invasive carcinoma at screening; or history of these results.

- 3.2.3 HGAIN (e.g., AIN 2 or 3, or perianal intraepithelial neoplasia grade 2 or 3) or invasive carcinoma at pre-entry on biopsy, or participant has a history of invasive carcinoma or any prior anal cytology result of HSIL or ASC-H.
- 3.2.4 Use of any systemic antineoplastic or immunomodulatory treatment, systemic corticosteroids for greater than 14 days, investigational vaccines, interleukins, interferons, growth factors, or IVIG within 45 days prior to study entry.
- 3.2.5 It is encouraged that standard of care vaccinations are not offered during the 2 weeks preceding plasma HIV-1 RNA measurements, and that standard of care vaccinations are not administered at the same time as the study vaccine. Routine vaccinations other than influenza vaccine that are administered after enrollment in the study should be given 1 month before or after HPV vaccination (or any visit where antibody titers are measured) during the study period. Influenza vaccination may be given within 1 week before or after HPV vaccination visits.
- 3.2.6 Expected use of any systemic antineoplastic or immunomodulatory treatment, systemic corticosteroids used for greater than 14 days, investigational vaccines, interleukins, interferons, growth factors, or IVIG during study followup. Hepatitis C co-infected subjects should not enroll in this study if they expect to initiate treatment for hepatitis C (e.g., interferons) during this trial.
- 3.2.7 Active drug or alcohol use or dependence that, in the opinion of the site Investigator, would interfere with adherence to study requirements.
- 3.2.8 Serious illness requiring systemic treatment and/or hospitalization within 45 days prior to entry.
- 3.2.9 Serious medical or psychiatric illness that in the opinion of the site Investigator will interfere with the ability of the subject to give informed consent or adhere to the protocol.
- 3.2.10 Subject is currently receiving anticoagulation therapy other than acetylsalicylic acid.
- 3.2.11 Inability to provide informed consent (and assent, if subject is under the age of 18).
- 3.2.12 Allergy to yeast or any of the components of Gardasil.
- 3.2.13 Prior splenectomy.
- 3.2.14 Hemophilia.
- 3.2.15 Prior receipt of Gardasil or other HPV vaccine.

3.3 Number of Subjects to be Enrolled

This study will enroll 150 subjects. A table of the accrual targets by ethnic and racial categories is found below.

Accrual Targets				
Ethnic Category	Sex/Gender			
	Females		Males	Total
Hispanic or Latino	0	+	30	= 30
Not Hispanic or Latino	0	+	120	= 120
Ethnic Category: Total of all subjects	0 (A1)	+	150 (B1)	= 150 (C1)
Racial Category				
American Indian or Alaskan Native	0	+	1	= 1
Asian	0	+	2	= 2
Black or African American	0	+	45	= 45
Native Hawaiian or other Pacific Islander	0	+	2	= 2
White	0	+	100	= 100
Racial Category: Total of all subjects	0 (A2)	+	150 (B2)	= 150 (C2)
	(A1 = A2)		(B1 = B2)	(C1 = C2)

3.4 Study Enrollment Procedures

Prior to implementation of this protocol, sites must have the protocol and protocol informed consent form(s) approved by their local institutional review board (IRB).

This study will be available for enrollment at all interested AMC and ATN sites that have been approved by the HPV Working Group. Approval will be based on the capacity to perform HRA. Sites must be registered with the AMC Operations and Data Management Center (ODMC) before they may enroll subjects.

3.4.1 Registration for Screening

After an informed consent form has been signed by the subject, the subject must be registered for screening (AMC-072, Segment A) on-line via the AMC AdvantageEDCSM Internet Data Entry System. After successful registration into screening, the subject will receive a nine-digit subject ID and will then enter the screening process (Screening and Pre-entry visits).

3.4.2 Enrollment

After the screening evaluations have been obtained and the subject is determined to be eligible, the participating site will complete the protocol-specific eligibility checklist and enroll the subject into AMC-072 Segment B (on-line via the AMC Internet Data Entry System). Enrollment should occur no more than 72 hours prior to the initiation of vaccination. (Enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system generated confirmation email will be sent to the enroller upon successful completion of the subject enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

Subjects must be enrolled into AMC-072 Segment B prior to receiving the first vaccination.

4.0 STUDY TREATMENT PLAN/PHARMACEUTICAL AGENT

4.1 Drug Regimen, Administration, and Duration

The vaccination schedule with quadrivalent HPV vaccine (0.5 mL vaccine by intramuscular [IM] injection) is at Day 1, Week 8, and Week 24.

4.1.1 Regimen

Day 1, Week 8 and Week 24

Quadrivalent HPV (Types 6, 11, 16, 18) recombinant vaccine, 0.5 mL, intramuscularly in the deltoid region of the upper arm or the higher anterolateral area of the thigh.

4.1.2 Study Product Administration

Quadrivalent HPV (Types 6, 11, 16, 18) recombinant vaccine will be administered as three separate 0.5 mL doses according to the visit schedule. The vaccine will be administered in the clinic by study personnel using aseptic technique during preparation and administration.

The vaccine is to be used as supplied; no dilution or reconstitution is necessary. Thorough agitation is required immediately prior to administration to maintain suspension of the vaccine. It is necessary to shake well before use. After thorough agitation, the suspension is a white, cloudy liquid. Inspect the suspension visually for particulate matter and discoloration prior to administration. Do not use the vaccine if particulates are present or it appears discolored.

The vaccine will be supplied as a 0.5 mL single-dose vial. Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe. Once the single-dose vial has been penetrated, use the withdrawn vaccine promptly, and discard the vial.

All injections should preferably be given in the non-dominant arm (or thigh), however, if this is not feasible, the dominant arm (or thigh) may be used. The vaccine must not be injected intravascularly, subcutaneously or intradermally.

Syncope may follow vaccination. Observe that subject for approximately 15 minutes after administration of the vaccine.

4.1.3 Expected Adverse Events

Please refer to the FDA-approved package insert for a comprehensive list of AEs. This package insert is available at www.gardasil.com.

Local reactions include pain, swelling, erythema, itching and bruising. Systemic reactions include syncope, fever, nausea and vomiting, dizziness, fatigue, headache, and chills. Other rare, but serious side effects reported with this vaccine that may be associated with this vaccine include hypersensitivity reactions and Guillain-Barre Syndrome.

4.2 Study Vaccine Formulation and Preparation

Store vials of Quadrivalent HPV (Types 6, 11, 16, 18) recombinant vaccine under refrigeration at 2° to 8° C (36° to 46°F). **Do not freeze**. Protect from light.

Each 0.5 mL dose contains approximately:

HPV 6 L1 protein	20 mcg
HPV 11 L1 protein	40 mcg
HPV 16 L1 protein	40 mcg
HPV 18 L1 protein	20 mcg
Amorphous aluminum hydroxyphosphate sulfate adjuvant	225 mcg
Sodium chloride	9.56 mg
L-histidine	0.78 mg
Polysorbate 80	50 mcg
Sodium borate	35 mcg
Yeast protein	< 7 mcg
Water	qs

4.3 Pharmacy: Study Vaccine Supply, Distribution, and Accountability

Quadrivalent HPV (Types 6, 11, 16, 18) recombinant vaccine will be supplied by Merck & Co., Inc. Gardasil is a commercial agent.

4.3.1 Study Vaccine Acquisition

Participating sites are to refer to the study drug request form located on the AMC ODMC web site (www.amcoperations.com).

4.3.2 Study Vaccine Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (DARF) (available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the Pharmaceutical Management Branch at 240-276-6575) or a site-specific form that captures the same elements as the NCI DARF.

4.3.3 Study Vaccine Transfers

Vaccine may not be transferred from one subject to another subject, from one center to another center, or from one protocol to another protocol.

4.3.4 Study Vaccine Return

Please refer to the agent return form for procedures regarding Gardasil return and disposal. The form is located on the AMC ODMC web site (www.amcoperations.com).

4.4 Concomitant Medications

To avoid adverse events (AEs) caused by drug interactions, sites must refer to the most recent package inserts for the study vaccine and concomitant agents whenever a concomitant medication is initiated or a dose is changed.

Sites must also refer to the most recent study product's package insert to access additional current information on prohibited and precautionary medications.

4.4.1 Required Medications

There are no required medications for subjects taking part in this study.

4.4.2 Prohibited Medications

Systemic antineoplastic or immunomodulatory treatment, systemic corticosteroids (of greater than 14 days duration), investigational vaccines, interleukins, interferons, growth factors, or IVIG.

Site staff must contact the Protocol Chair(s) for guidance if a subject requires a restricted medication prior to a study vaccine visit or a visit that is measuring HPV antibody titers (i.e., screening and Weeks 28, 52, 78 and 104).

Note: If a prohibited medication is taken after completion of all HPV vaccination visits, contact the Protocol Chair(s) first to discuss premature discontinuation.

4.4.3 Precautionary Medications

It is encouraged that standard of care vaccinations are not offered during the 2 weeks preceding plasma HIV-1 RNA measurements, and that standard of care vaccinations are not administered at the same time as the study vaccine. Routine vaccinations other than influenza vaccine that are administered after enrollment in the study should be given 1 month before or after HPV vaccination (or any visit where antibody titers are measured) during the study period. Influenza vaccination may be given within 1 week before or after HPV vaccination visits.

Initiation of antiretroviral therapy is not prohibited in this protocol for subjects who are not receiving antiretroviral therapy at study entry. Subjects should not be enrolled if they have known plans to initiate antiretroviral therapy prior to Week 28.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Schedule of Evaluations

Please see [Appendix I, Schedule of Evaluations](#).

5.2 Timing of Evaluations

5.2.1 Screening and Pre-Entry

Screening evaluations must occur prior to the subject starting any study medications, treatments, or interventions.

Screening and pre-entry evaluations to determine eligibility must be completed within 45 days prior to study entry unless otherwise specified. The screening and pre-entry visit may be combined.

In addition to data being collected on subjects who enroll into the study, demographic, clinical, and laboratory data on screening failures (that are available) will be captured in a screening log.

ACSR Samples

Although it is optional, blood and fresh-frozen tissue obtained before the start of therapy and at Week 104 will be requested whenever possible for research purposes. This should be sent to the AIDS and Cancer Specimen Resource (ACSR) for donation ([Appendix XV](#)) and REQUIRES a separate consent form (and assent, if applicable). (See [Appendix XIII](#) and [Appendix XIV](#) for ACSR consent and ACSR assent forms).

The ACSR tissue biopsy may be collected at week 104 even if a baseline ACSR tissue biopsy donation was not collected. The ACSR tissue biopsy may only be collected with the participant's consent, if there are suspected lesions observed during HRA (i.e., not from normal areas), and must be a separate specimen from the diagnostic biopsy.

It is expected that anal tissue donated to ACSR may be evaluated for HPV detection and typing, gene expression by microarray analysis and potentially other research assays as additional correlative science studies are developed. These evaluations will not be done in real time.

5.2.2 On-Study Evaluations

Evaluations must occur after subject registration. Study visits must be scheduled on the weeks indicated in the Schedule of Evaluations ([Appendix I](#)) ± 7 days through Week 8. Study visits scheduled for Weeks 24 and 28 must be scheduled ± 10 days. Study visits scheduled for Weeks 52, 78 and 104 must be scheduled ± 28 days. Telephone follow-up (Section 5.3.11) must occur within 24-48 hours post vaccination at Day 1, Week 8, and Week 24.

Effort should be made to keep subjects on the proper vaccination schedule (Day 1, Week 8 \pm 7 days, and Week 24 \pm 10 days). If subjects cannot be seen within the protocol specified windows, then these visits may be conducted outside the window and the subsequent vaccination visit should be adjusted. For example, if vaccine dose #2 is delayed from Week 8 to Week 10, all subsequent visits should be delayed by 2 weeks so that vaccine dose #3 will occur at Week 26 (Week 24 + 2 weeks). The Protocol Chair(s) and AMC ODMC should be notified of these protocol deviations and the site must complete a Protocol Deviation Form documenting all protocol deviations.

The Week 28 visit will collect samples for the primary immunogenicity endpoint. This visit should be conducted 30 days (+/- 10 days) after the third vaccination. If a subject's third vaccine (i.e., Week 24 visit) was delayed until Week 27, then the Week 28 visit should be conducted 30 days after the third vaccine (approximately Week 31 in this example). All subsequent visits after the primary immunogenicity endpoint (Weeks 52, 78 and 104) should occur according to the original planned schedule.

Study Entry

Entry evaluations must occur at least 24 hours after screening evaluations and within 45 days of screening evaluations. Evaluations must be done prior to the subject taking any study treatment. Subjects must begin study treatment within 72 hours after registration.

5.2.3 Evaluations for Subjects Who Do Not Start Study Treatment

Registered subjects who withdraw from the study prior to starting study treatment should have screening, study entry, and off-study forms completed and keyed. No further follow-up is required for these subjects.

5.2.4 Premature Treatment Discontinuation Evaluations

Subjects who prematurely discontinue study treatment will be asked to continue in the study in an off-treatment/on-study status and receive all study evaluations per the schedule of evaluations through to completion of the study. No extra evaluations are required at the time of the treatment discontinuation. The Off-Treatment Form should be completed.

5.2.5 Premature Study Discontinuation Evaluations

Subjects who prematurely discontinue from the study will have the premature study discontinuation evaluations indicated in the schedule of evaluations performed prior to being taken off the study. The Off-Treatment and Off-Study Forms should be completed.

5.3 Special Instructions and Definitions of Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. All data requested by the study should be recorded in the source documents. All

stated evaluations will be entered on the appropriate CRF via the AdvantageEDCSM Internet Data Entry System unless otherwise specified. Quality assurance of data should follow the standards prescribed by the network under which the site is enrolling subjects (AMC or ATN).

5.3.1 Documentation of HIV-1

HIV-1 infection as documented by any federally approved, licensed HIV test performed in conjunction with screening (ELISA, Western blot or other approved test). Alternatively, this documentation may include a record that another physician has documented that the patient has HIV based on prior ELISA and western blot, or other approved diagnostic tests. If the participant's HIV status is documented by an outside physician, the protocol team strongly recommends obtaining a copy of the HIV laboratory reports from this physician. All confirmatory tests and the physician's note must be on file before the participant is enrolled. In the rare circumstance where only an outside physician's note with no supporting laboratory documentation is available, the local site should have additional tests performed to verify the participant's HIV status. One of the following additional tests should be performed:

- A rapid HIV test
- ELISA and Western blot
- Chemiluminescence immunoassay and Western blot
- HIV RNA > 2000 copies/mL
- HIV antigen test

5.3.2 Medical/Medication History

Medical History

The following must be in the CRF:

- History of receptive anal intercourse ever
- History of genital or anal condyloma
- History of prior anal cytologies or anal biopsies
- History of systemic cytotoxic chemotherapy and/or radiation
- History of splenectomy or hemophilia
- Presence of chronic hepatitis b or c

Other aspects of the medical history including allergies to any medications should be in the source documents only.

Medication History

The following must be in the CRF:

- Actual or estimated start date of each agent that is part of the current HAART therapy.

A medication history must be present in source documents, including:

- HIV treatment history in the 6 months prior to study entry, including any antiretroviral medication.
- Any vaccines received by the participant 45 days prior to study entry.

- Treatment history of any prescription medications, immune modulating herbal supplements, and over the counter medication taken within 45 days prior to study entry, including actual or estimated start and stop dates.
- History of Gardasil or other HPV vaccine use.

5.3.3 Concomitant Medications/Antiretroviral Medication Modifications

Concomitant Medications

Use of any systemic antineoplastic or immunomodulatory treatment, systemic corticosteroids, investigational vaccines, interleukins, interferons, growth factors, or IVIG should be documented in the CRFs.

Any prescription medications that have been initiated since the last report should be documented in the source documents only.

Antiretroviral Medications

Any modifications to antiretroviral medications since the last report will be entered on the CRFs. Modifications would include more than 7 consecutive days of missed antiretroviral medications. Modifications do not include change in current antiretroviral medication dose or formulations.

5.3.4 Study Treatment Record

All modifications to study vaccine including initial doses and permanent discontinuation of treatment will be entered on the CRFs.

5.3.5 Nadir CD4+ Cell Count

The subject's prior nadir CD4+ cell count (absolute value and date) should be documented, when possible, with a copy of the nadir CD4+ cell count report and entered on the CRF. If this documentation is not available, then subject recollection will suffice. For subjects who do not know the exact nadir value and for whom there is no source documentation, then recall of the categorical nadir (e.g., <50, <100, <200 cells/mm³) will suffice.

5.3.6 Complete Physical Exam

This should be documented in the source documents only. This examination includes at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; and Karnofsky performance test. The complete physical exam will also include signs and symptoms, height, weight, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure).

5.3.7 Clinical Assessments

Targeted Physical Exam

This should be documented in the source documents only. A targeted physical examination is to include vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the subject has experienced since the last visit. The vaccination site should be examined for erythema, swelling, tenderness or lumps up to Week 28. Staff should inquire about symptoms and examine the relevant areas, as indicated. Staff should inquire specifically about signs and symptoms of muscle aches, skin rashes, pruritus or redness.

The penis, scrotum and perianal area will be examined for signs of HPV-related lesions. The presence or absence of penile/scrotal/perianal condyloma will be recorded on the CRFs. Anal cytology and HRA with biopsy of visible disease will be performed to assess anal HPV-associated disease. Sampling of the penis/scrotum, perianal area and the anal canal for HPV DNA and other sexually transmitted agents will be performed. HRA and anal cytology are required assessments at baseline and Weeks 28, 52, 78, and 104. Only visual inspection of the penis, scrotum, and perianal area are required at Week 8 and Week 24.

Staff should inquire about symptoms of sexually transmitted diseases such as genital ulcer, dysuria, penile discharge, rectal pain or discharge, rash or sore throat. Staff should provide subjects with counseling and condoms to avoid acquisition of sexually transmitted diseases or new strains of HIV, and to avoid spread of HIV infection at each visit.

Signs and Symptoms

All signs and symptoms that begin during or after the entry visit should be recorded in the CRF regardless of grade. Any signs and symptoms that began prior to the entry visit should be recorded only if there is a significant worsening of the sign or symptom. After Week 32, only signs or symptoms ≥ grade 3 or signs and symptoms that are possibly, probably or definitely related to study vaccine should be recorded.

This study will utilize the CTCAE Version 4.0 (Common Terminology Criteria for Adverse Event reporting) for grading of clinical or laboratory events. (See Section 7.0)

Diagnoses

Record all diagnoses identified by the CTCAE Version 4.0 criteria (see Section 7.0 for details) for clinical events and other diseases. Furthermore, any diagnosis of a cellulitis, abscess, or other infection at the vaccination site should be recorded.

Vaccine Report Card

Subjects should be given a Vaccine Report Card ([Appendix XI](#)) to take home and fill out after each vaccination. The subject should record an oral temperature 4 hours

after vaccination and then daily for 4 more days. They should indicate whether redness, swelling, or pain or tenderness has occurred 4 hours after vaccination and then daily for 4 more days. They should record any adverse event for up to 15 days after vaccination to include local and systemic reactions. They should be instructed to contact the study nurse for any fever or moderate/severe symptoms. The nurse will call them within 24-48 hours of vaccination. The subject should be instructed to return the Vaccine Report Card at the next visit following each vaccination (Weeks 8, 24 and 28).

5.3.8 Laboratory Evaluations (See [Appendix I](#) for timing of evaluations.)

This study will utilize the CTCAE Version 4.0 for Common Terminology Criteria for Adverse Event reporting. Record all Grade ≥ 2 laboratory values (except for CD4 cell counts) as AEs. All laboratory toxicities that led to a change in treatment, regardless of grade, must be recorded.

- Hematology - CBC with differential
- Liver Function Tests - AST (SGOT), ALT (SGPT), and total bilirubin
- Anal cytology (See [Appendix V](#), Anal Cytology Sampling Procedures)
- Anal HPV DNA PCR (See [Appendix VI](#), HPV DNA PCR Specimen Collection and Shipping)
- HPV strain variant analysis among those who are positive for these types in more than one sample at any visit or over time.
- HPV 16, 18, 31, 6 or 11 DNA quantitation using quantitative PCR before and after vaccination among those who are HPV-positive at baseline.
- High resolution anoscopy (HRA) (See [Appendix VII](#))
- Oral testing for HPV DNA (See [Appendix VIII](#))
- Urine specimens for GC and Chlamydia using nucleic acid amplification test (NAAT) (performed locally at sites)
- Penile, scrotal and perianal area sampling for HPV DNA PCR
- AIN or condyloma biopsies diagnosed during the study will be analyzed for the presence of HPV DNA using PCR.

5.3.9 Immunologic Studies

To document eligibility for those subjects who are not on antiretroviral therapy, CD4+ level must be equal or greater than 350 cells/mm³ within 90 days prior to study entry from a laboratory that possesses a CLIA certification or equivalent. CD4+/CD8+ will be obtained from all subjects within 90 days prior to study entry and at Week 28.

Serum HPV antibody testing

A serum sample will be drawn for HPV antibody testing as well as storage for future testing. The HPV antibody test will be performed by the Merck Research Laboratory. Please refer to [Appendix IX](#) for information regarding HPV antibody specimen collection and shipping procedures.

5.3.10 Virologic Studies

Plasma HIV-1 RNA

On-study plasma HIV-1 RNAs will be done in real time. Plasma HIV viral load will be obtained within 90 days prior to study entry and at Week 28.

5.3.11 Telephone Follow-Up

Each subject (or legal guardian) will be contacted by the study nurse by telephone 24 to 48 hours following each vaccination to determine if any side effects have occurred. Information from the telephone contact will be recorded. If a subject experiences any side effects (including fever) that are grade 3 or 4, or if he has edema (swelling), erythema (redness), or induration of grade 2, the subject should be scheduled to come into the clinic as soon as possible, for an evaluation that includes a targeted physical examination focused on the area involved.

5.3.12 Smoking Status/Recent Sexual History /Risk Perception And Knowledge Questionnaire

Each subject will be given a Questionnaire to determine their smoking status, recent sexual history and risk perceptions about HPV **after** receiving each vaccination (Day 1, Week 8 and Week 24) and at Weeks 52, 78 and 104 (See [Appendix I](#)). Sites should ensure that the Questionnaire includes the subject's 9-digit study number prior to giving the Questionnaire to the subject. Subjects will fill out the Questionnaire, place the completed Questionnaire in an envelope and seal it. Site should mail completed Questionnaires to:

**ATTN: AMC Operations and Data Management Center
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850**

5.4 Dose Modification/Toxicity Management

5.4.1 Management of Injection Site and Allergic Reactions

Local and systemic reactions will be graded according to the CTCAE Version 4.0 for Common Terminology Criteria for Adverse Event reporting.

5.4.1.1 Injection Site Reactions

- Swelling or redness at the injection site
- Pain or tenderness, or other reactions at the injection site

For injection site reactions judged to be severe, the safety review team should be notified within 24 hours and further vaccines should not be given to that subject prior to consultation with Protocol Chair/Co-chairs.

For injection site reactions judged to be life-threatening, the safety review team should be notified within 24 hours and no additional vaccinations shall be given to that subject.

5.4.1.2 Systemic Reactions occurring within 48 hours after vaccination

- Fever or chills
- Malaise or fatigue
- Headache or pain (e.g., myalgias or arthalgias)
- Nausea or vomiting
- Allergic reactions

The safety review team should be contacted within 24 hours for any systemic grade 3 or 4 reactions (e.g., elevated temperatures following vaccination) thought definitely, possibly, or probably related to vaccination. Further vaccines should not be given to that subject prior to consultation with the Protocol Chair/Co-chairs.

Subjects who are allergic to yeast or to any component of the vaccine should not receive quadrivalent HPV vaccine.

Clinically significant adverse reactions and other problems related to vaccines will be reported to the Vaccine Adverse Event Reporting System (VAERS), which is maintained by the FDA and CDC (<http://vaers.hhs.gov/>).

5.4.2 Other Adverse Events

For toxicities not specifically addressed above, the following guidelines should be used for the management of AEs:

Grade 1 or 2 Toxicity/AE

Subjects who develop a grade 1 or 2 AE may continue study vaccine. For instructions regarding subjects experiencing grade 1 or 2 AEs who choose to permanently discontinue study treatment or study participation, see Sections 5.2.4 and 5.2.5.

Grade 3 or 4 Toxicity/AE

Subjects who develop a grade 3 or 4 AE should be reevaluated for that toxicity until the AE returns to grade ≤ 2 . The study vaccine may be given at the discretion of the site investigator. If the same grade 3 or 4 AE recurs and is considered by the investigator to be possibly related to the study vaccine, the study vaccine must be permanently discontinued. If, in the investigator's opinion, the AE has NOT been caused by the study vaccine or if the event is an asymptomatic laboratory abnormality, study treatment may continue.

For instructions regarding subjects experiencing grade 3 or 4 AEs that result in permanent discontinuation of study vaccine or study participation, see Sections 5.2.4 and 5.2.5. These subjects should be followed weekly until resolution of the AE.

6.0 CRITERIA FOR DISCONTINUATION

6.1 Permanent Treatment Discontinuation

- Drug-related toxicity (see Section 5.4 for details of toxicities requiring treatment discontinuation).
- Development of an allergy or systemic sensitivity to study medication.
- Completion of treatment as defined in the protocol.
- Request by subject to terminate treatment.

6.2 Premature Study Discontinuation

- Request by the subject to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.
- The subject is judged by the Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the AMC, ATN, IRB, Office for Human Research Protections (OHRP), NCI, NICHD, investigator, or pharmaceutical supporter.
- Clinical reasons believed life-threatening by the site Investigator, even if not addressed in the toxicity section of the protocol.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocol_Development/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.1 Classification of AEs by Severity and Relationship to Study Vaccine Administration

Adverse Event

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Life-Threatening Adverse Event

Any AE that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.

Serious Adverse Event (SAE)

Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, in the Investigator's opinion, or a congenital anomaly/birth defect.

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

Toxicity

Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

Unexpected Adverse Event

Any AE that is not listed in the package insert, protocol, or informed consent form.

CTEP Adverse Event Reporting System(CTEP-AERS)

An electronic system for expedited submission of AE reports.

Attribution

The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:

Definite	The AE is clearly related to the investigational agent(s).
Probable	The AE is likely related to the investigational agent(s).
Possible	The AE may be related to the investigational agent(s).
Unlikely	The AE is doubtfully related to the investigational agent(s).
Unrelated	The AE is clearly NOT related to the investigational agent(s).

7.2 Routine Reporting of AEs with Investigational Agents/VAERS

An investigational agent is one being studied under an Investigational New Drug Application (IND). In some instances, a commercial agent may also be considered investigational when used under an IND.

All AEs, regardless of severity, and whether or not ascribed to the study vaccine administration, will be recorded in the appropriate section of the CRF. After Week 32, only SAEs and AEs or symptoms \geq grade 3 or symptoms that are possibly, probably, or definitely related to the study vaccine should be recorded. Subjects withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

AEs reported through CTEP-AERS must also be reported in routine study data submissions.

Clinically significant adverse reactions and other problems related to vaccines will be reported to the Vaccine Adverse Event Reporting System (VAERS), which is maintained by the FDA and CDC (<http://vaers.hhs.gov/>).

7.3 Expedited AE Reporting

7.3.1 Expedited AE Reporting through CTEP-AERS

Expedited AE reporting for this study will occur via CTEP-AERS (Adverse Event Reporting System) accessed via the Cancer Therapy Evaluation Program (CTEP) home page. (<http://ctep.cancer.gov>). Expedited reporting requirements are outlined in the table below. CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Protocol Study Chair, Principal Investigator at the local AMC treating institution, and AMC Operations Center. CTEP-AERS provides a copy feature for other e-mail recipients. All reported SAEs will be reviewed by the Protocol Chair to determine if further action is necessary.

A 24-hour notification is to be made to the AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into CTEP-AERS by the original submitter at the site.

Expedited Reporting Timelines for Adverse Events that occur within 8 Weeks¹ of the Last Dose of the Investigational Agent on Phase 2 and 3 Studies

	1	2	2	3		3		4 & 5	4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

¹Adverse events with attribution of possible, probable, or definite that occur greater than 8 weeks after the last dose of treatment require reporting as follows:

24-hour notification followed by complete report within 5 calendar days for:

- Grade 3 events at least possibly related to treatment
- Grade 4 and Grade 5 unexpected events

Complete SAE report within 10 calendar days:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

²Although 24-hour notification is not required for death clearly related to progressive disease a full report is required as outlined in the table.

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7.3.2 Expedited AE Reporting to Merck

All SAE reports submitted through CTEP-AERS that are at least possibly attributed to study vaccine administration will be forwarded to designated Merck personnel by the AMC Operations Center.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

The sample size considerations are based on estimation of the incidence of HPV infection/anogenital disease. This is an open-label trial in which the beneficial effects of the vaccine are expected to be limited to those who are naive to one or more of the HPV vaccine types. Analyses will be conducted for HPV 6, 11, 16 and 18 separately. The study will evaluate the impact of vaccination on anogenital disease associated with vaccine HPV types: anogenital disease is defined as intra-anal and external ano-genital lesions further defined as low-grade (condyloma/intraepithelial neoplasia grade 1) and high-grade lesions (intraepithelial lesions grades 2-3)

The incidence of HPV infection/anogenital disease will be estimated in four groups based on all four types combined and on a type-specific basis:

- 1) Seronegative/DNA negative
- 2) Seronegative/DNA positive
- 3) Seropositive/DNA negative
- 4) Seropositive/DNA positive

Our plan is to administer the vaccine to all study participants. The power estimates are based on an anticipated incidence of HPV-associated disease without vaccine and determining whether we can detect a lower rate with the vaccine. If we assume hypothetically that the incidence of persistent HPV infection w/o vaccine is 10 per 100 PY and the expected incidence of HPV-associated disease is 5 per 100 PY, then the attached table shows the effect size and associated lower rate of infection that can be detected with the anticipated numbers of patients for a “per protocol” population for each HPV type. No adjustments were made for the fact that we are looking at four distinct HPV types.

8.2 Endpoints

8.2.1 Primary Endpoints

- Any incident AIN or anal/perianal condyloma associated with HPV 16, 18, 6 or 11 DNA (as determined by PCR analysis of the anal tissue biopsy). No biopsies will be taken of penile/scrotal lesions and incident penile/scrotal condyloma will be considered an endpoint if associated with a positive penile/scrotal sample for HPV 6, 11, 16 or 18 DNA at the same visit.
- Diagnosis of HGAIN related to vaccine HPV types at any time during the study is also a study endpoint. Subjects with HGAIN should be treated but should remain in follow-up during the study per the routine study calendar.
- Any persistent anogenital infection with HPV 16, 18, 6 or 11 DNA, defined as having positive PCR results with a specific HPV type at 2 or more consecutive visits. Persistent HPV DNA positivity is defined as detection of the same HPV type in any of the samples at a given visit over at least 2 consecutive visits. To be considered eligible for analysis at least one of the specimens at a given visit must be positive for beta-globin DNA.

8.2.2 Secondary Endpoints

- Occurrence of grade ≥ 3 AEs that are possibly, probably or definitely related to the vaccine.
- Longitudinal changes in plasma HIV-1 RNA and CD4+ cell count from Baseline.
- Level of HPV antibodies to types 6, 11, 16 and 18, at Baseline, one month after the completion of HPV vaccination series and Weeks 52, 76 and 104.

8.2.3 Tertiary Endpoints

- Level of HPV DNA before and after vaccination.
- Type and level of HPV DNA in the oral cavity
- HPV strain variation before and after receipt of the quadrivalent HPV vaccine.
- Baseline prevalence and incidence of penile gonorrhea and Chlamydia infection.
- Change in young men's risk perceptions, sexual behaviors, and STI diagnosis after HPV vaccination.

8.3 Sample Size and Accrual

Based on the existing literature among young HIV-positive MSM (Moscicki AB AIDS. 2003;17:311-20) it was assumed that the baseline prevalence of HPV 16 DNA would be 14% DNA-positive, and an additional 14% was estimated to be seropositive. Therefore 72% would be eligible for PPE analysis. For HPV18, we assumed 0% to be DNA-positive and 10% to be seropositive, therefore 90% would be eligible for PPE analysis. HPV 6 and HPV 11 were presented combined in the paper at a total of 23%. We can assume for our purposes that each was found at 16% for 6 and 8% for HPV 11. Assuming another 16% and 8% to be seropositive for 6 and 11, respectively, therefore we assume that 68% would be available for PPE analyses for HPV 6 and 84% for HPV 11.

Data on incidence HPV infection or disease are available on the placebo group from the Merck 020 study. The vaccine will be considered to have a preventive effect if it reduces the anticipated incidence of HPV infection/anogenital disease by 75% overall in the study population.

It is anticipated that 150 patients will be recruited and followed for two years for a total of 300 person-years. The ITT Merck placebo rates were used to determine the number of events (HPV-type specific AIN or persistent infection) that are expected with 200 person-years. If the vaccine has a 75% efficacy rate, then the number of events expected on the vaccine would be 25% of that expected using the Merck rates. Using the normal approximation to the Poisson distribution with the standard deviation based on the Merck rate (conservative approach), there will be 99% power to detect the following differences at the one-sided 0.10 significance level with 150 patients followed for 2 years.

HPV-related AIN

	Merck Placebo data		Vaccine Group		Standard deviation	Effect Size
	AIN-rate per 100 PY	Expected AIN events (300 PY)	AIN-rate per 100 PY	Expected AIN events (300 PY)		
HPV-6	7.30	21.90	1.83	5.48	4.68	3.51
HPV-11	3.80	11.40	0.95	2.85	3.38	2.53
HPV-16	2.70	8.10	0.68	2.03	2.84	2.14
HPV-18	1.60	4.80	0.40	1.20	2.19	1.64

HPV-related Persistent Infection

	Merck Placebo data		Vaccine Group		Standard deviation	Effect Size
	Persistent infection rate per 100 PY	Expected Persistent infection events (300 PY)	Persistent infection rate per 100 PY	Expected Persistent infection events (300 PY)		
HPV-6	10.70	32.10	2.68	8.03	5370	4.22
HPV-11	4.30	12.90	1.08	3.24	3.59	2.70
HPV-16	5.60	16.80	1.40	4.20	4.10	3.07
HPV-18	3.80	11.40	0.95	2.85	3.38	2.53

It is anticipated that there will be 100 HPV-type naïve patients for each HPV type. If the vaccine has a 75% protective effect, then the following table shows the upper the estimated upper bound of the 90% confidence interval for the incidence of HPV-specific AIN and persistent infection.

HPV-related AIN

	Incidence on vaccine (per 100 PY)	Upper 90% Confidence Limit (per 100 PY)
HPV-6	1.83	2.00
HPV-11	0.95	1.07
HPV-16	0.68	0.75
HPV-18	0.40	0.48

HPV-related Persistent Infection

	Incidence on vaccine (per 100 PY)	Upper 90% Confidence Limit (per 100 PY)
HPV-6	2.68	2.88
HPV-11	1.08	1.21
HPV-16	1.40	1.55
HPV-18	0.95	1.07

To determine if there will be sufficient numbers of HPV-naïve patients for each type, the study team will review the distribution of HPV types after a total of 100 patients have enrolled in the study. If it appears that for any of the HPV types, that there will be fewer than 67% of the patients that are naïve to that type, an amendment may be submitted to increase

the number of patients to ensure that there are 100 naïve patients per type. At the time of the amendment the scientific rationale for the sample size increase (including the use of the Merck Placebo data as historical control) will be re-evaluated.

8.4 Safety Analysis

Regarding safety, the adverse event rate will be assessed for the combined groups, and will include all subjects who receive at least one dose of study vaccine. We will report the adverse event rate as defined by 8.2.2 with a corresponding upper bound of a one-sided 95% confidence interval. With 100 evaluable patients, if no more than eight patients experienced an adverse event as defined by Section 8.2.2, the upper bound of the one-sided 95% confidence interval for the AE rate would be below 15%. There is 80% power to reject the null hypothesis that the AE rate is 6.5%. All safety endpoints will be reviewed by a team of AMC and ATN medical monitors. The final adjudication for the relationship to vaccine (unrelated, unlikely, possible, probable, or definite) will be made by this team. We will also report the adverse event rate and corresponding confidence interval for adverse events regardless of attribution to study vaccine.

We will also report injection site reactions and systemic reactions specified in Section 5.4.1.1 and 5.4.1.2 of all grade.

8.5 Monitoring

The study will be reviewed at least quarterly by a team of AMC and ATN medical monitors. The study team will receive monthly reports on accrual and study conduct, and the NCI Clinical Representative will review a safety report every 3 months.

The first AMC/ATN Medical Monitor team review will be after the first 30 subjects have reached Week 28. The AMC/ATN Medical Monitor team will be provided data on accrual, retention, and occurrence of adverse events as defined by the secondary endpoints.

The occurrence of at least two adverse events as defined by Section 8.2.2 or a single grade 4 or 5 adverse event that is at least possibly related to study vaccine will cause the study to halt enrollment and further vaccinations. The study will restart only after a review of available safety data and SAE reports by the safety review team. If consensus about restarting the study is not reached among these members, then the decision will be made by the AMC Executive Committee. This process will be repeated after every 2 adverse events as defined by Section 8.2.2 or after each grade 4 or 5 adverse event that is at least possibly related to study vaccine.

8.6 Primary, Secondary and Tertiary Analyses

8.6.1 Primary

The primary analysis of the study on incident AIN or condyloma will be performed among those who are naïve to a given HPV type and who complete the vaccination series per protocol, compared with subjects who are not naïve. Specifically, we will report the prevalence of anal condyloma or AIN at weeks 28, 52, 76 and 104. To be counted as a case, the anal biopsy must be positive for HPV 6, 11 16 or 18 DNA. No penile/scrotal biopsies will be taken and a case of incident penile/ scrotal condyloma

will be defined as clinical diagnosis of condyloma along with a positive HPV DNA result from the penile/scrotal specimen on the same day for one or more of the four HPV vaccine types. One set of primary analyses will be performed combining all cases positive for HPV 16, 18 and 6 or 11. Another set of analyses will be done on HPV 16, HPV 18 and HPV 6- or 11-associated lesions individually.

The primary analysis on prevention of persistent anal HPV infection will be performed among those who are naïve to a given HPV type and who complete the vaccination series per protocol, compared with subjects who are not naïve. A combined endpoint of persistent HPV 16, 18, 6 or 11 will be analyzed, as will persistent anal HPV 16, HPV 18 and HPV 6 or 11 individually.

We will obtain all available abnormal cytology and histology slides (pre-entry and post-entry) and 10% of normal cytology slides for central pathology review. A revised rate of incident condyloma or AIN after vaccination will be reported excluding those subjects with pre-existing high grade AIN at pre-entry or week 28 as judged by central review.

Using the incidence rates of HPV 6/11/16/18 - related AIN and anal cancers, persistent infection and DNA detection from the placebo group of a recently completed study (REF) in a Poisson distribution, the probability of detecting the results from the current trial will be estimated to determine if they are consistent with the previously reported placebo rates. It is anticipated that these analyses will be done for each HPV type. For the analysis of AIN and anal cancers, analyses will also be performed by lesion type. A one-sided significance level of 0.10 will be used for this analysis. No adjustments for multiple testing are planned.

8.6.2 Secondary

The safety analysis on the study AEs described in the primary endpoint will be performed according to section 8.4. For a safety analysis, the rate of AEs of grade 2 or higher will be estimated with a one-sided 95% CI. In addition, the changes in HIV RNA and CD4+ count from baseline at the scheduled measurement times will be summarized for all the subjects.

Detectable Ab response at Week 28 will be performed by HPV type (6, 11, 16 and 18) on the subjects who are seronegative and HPV DNA PCR-negative for that type at baseline and complete the vaccination series per protocol. The type-specific Ab response rates will be estimated with one-sided 95% CI's to specify the lower bounds. A secondary analysis will include only those subjects who are HPV DNA PCR negative at entry and Week 28.

The antibody response will also be analyzed on all study subjects who are seronegative for that type at baseline, as an intent-to-treat analysis. In addition, the Ab titer (as a continuous measure) at the scheduled times will be summarized using descriptive statistics for the subjects who are seronegative at baseline, for each HPV type (6, 11, 16, 18). Also, the Ab titer changes from baseline will be summarized for each of the four HPV types, for the subjects who are seropositive for that type at

baseline. We will also describe the antibody response among subjects who are HPV DNA PCR positive at baseline.

A logistic regression model will be developed to assess the effect of baseline and nadir CD4+ count, and age on Ab response to type 16 or 18 - depending on the baseline serostatus - using all study subjects. Note that subjects who initiate, discontinue, or modify antiretroviral therapy during the trial will not be excluded from these analyses.

8.6.3 Tertiary

Incident infections will be defined as HPV infections found after Week 28 with no evidence for prior infection: the type was not present at screening, entry or Week 28; and subjects were seronegative for that type at entry. We will also report reactivations/reinfections defined as HPV infections found after Week 28 that were not present at Week 28 among subjects with a prior history of that HPV type: presence of that type at screening or entry; or seropositivity at entry. For each HPV type, the proportion of study participants who develop a new HPV infection and the proportion who report reactivations/reinfections will be estimated using the binomial proportion and its 95% confidence interval. We will also describe the cytological and histological abnormalities observed at baseline.

In tertiary analyses, we will use descriptive statistics to characterize changes in the level of anogenital and oral HPV types 16, 18, 31, 6 and 11 at screening, entry and at all other time points at which DNA is collected. Significant changes will be defined as those more than one-half log difference from the previous specimen.

We will also describe the ongoing sexual exposure to HPV in the study population. Specifically, we will report the total number of sex partners (male and/or female), receptive anal sex partners, and active oral sex partners at study entry and every 6 months thereafter. In exploratory analyses, we will correlate these variables with incident HPV infections in the mouth and anus.

We will perform HPV strain variant analysis of samples positive for HPV 16, 18 and 31 at more than one visit to determine if the same variant is present in different anatomic locations and over time at the same location.

We will assess the prevalence of urinary gonorrhea and Chlamydia trachomatis infection at baseline and at all visits where samples are collected for GC and Chlamydia, and their relationship with prevalent and incident anogenital HPV infection and anal condyloma or AIN.

We will determine the effect of vaccination on young men's risk perceptions, sexual behaviors, and STI diagnosis. Participants will fill in the risk perceptions and knowledge survey ([Appendix XII](#)). Descriptive analyses will characterize subjects' risk perceptions, knowledge about HPV, sexual behaviors (e.g., condom use with sexual intercourse, number of sexual partners over prior 3 months) at study entry (immediately after vaccine dose #1), Week 8 (after vaccine dose #2), Week 24 (after vaccine dose #3), Week 52, Week 78, and Week 104.

Univariate analyses will be conducted to determine whether subject characteristics and HPV knowledge are associated significantly with risk perceptions after vaccine dose #1, and also whether knowledge and risk perceptions immediately post-vaccination are associated significantly with sexual behaviors or STI diagnosis at each of the follow-up visits.

In order to determine whether attitudes immediately post-vaccination are associated with behaviors and STI diagnosis at the four follow-up time points, we will use correlated logistic regression or generalized estimating equation (GEE) models with attitudes as the independent variables and behaviors or STI diagnosis as the dependent variables. GEE is a useful technique for dealing with repeated categorical data and is commonly used in situations where an identical measurement (behaviors or STI diagnosis) is repeatedly taken on the same subject. Repeated measurements induce a variance/covariance structure that can be utilized in the analysis, for example, the most general (unstructured) variance/covariance structure. Therefore, in addition to the odds ratios, the 10 variance/covariance parameters of the 4x4 variance/covariance matrix (since we have 4 time points) will be estimated.

If these parameters were found to be inestimable, then a Toeplitz structure (equi variance/covariance parameters along the diagonals), with four variance/covariance parameters, would be used.

We will also use linear mixed models to examine trends in sexual behaviors over time, and to compare trends in sexual behaviors over time in subjects who hold specific attitudes immediately post-vaccination vs. those who do not, taking into account all time points after vaccination. These models will also control for variables associated in univariate analyses with sexual behaviors or STI diagnosis. Linear mixed models take into account the repeated measures which also induce a variance/covariance structure that can be utilized in the analysis. Similar models will be used with STI diagnosis as the outcome variable.

9.0 DATA COLLECTION AND MONITORING

9.1 Records to Be Kept

CRFs will be provided for each subject via the AMC AdvantageEDCSM Internet Data Entry System upon enrollment. Subjects must not be identified by name on any study documents. Data will be recorded on the CRFs using the unique subject identification number assigned at registration. Sample CRFs will be available on the AMC ODMC web site (www.amcoperations.com).

9.2 Role of Data Management

Instructions concerning the recording of study data on CRFs will be provided by the AMC ODMC. The AMC Internet Data Entry System User's Guide can be found on the AMC ODMC web site (www.amcoperations.com). Each site is responsible for keying the data in and submitting the forms according to the target submission dates set forth by the AdvantageEDCSM system.

It is the responsibility of the AMC ODMC to assure the quality of computerized data for each AMC study. This role extends from protocol development to generation of the final study databases.

9.3 Clinical Site Monitoring and Record Availability

This protocol will follow the AMC Data Safety Monitoring Plan (see [Appendix X](#)).

10.0 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject (or parent, legal guardian, or person with power of attorney for subjects who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record. A signed assent form will be obtained from all subjects < 18 years of age.

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the NCI, the NICHD, the OHRP, or the pharmaceutical supporter(s) or designee.

10.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCI, the NICHD, the pharmaceutical supporter(s), the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected.

10.4 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Clinical Trials Consortium (AMC) and the NICHD-sponsored Adolescent Trials Network (ATN). As part of their contractual obligations, each participating site within the AMC/ATN and the AMC/ATN as a whole is required to assure that the participation of minority subjects reflects the percentage representation of these populations in their geographic region and, for the AMC/ATN, the United States as a whole. As such, it is expected that the representation of subjects on this trial will reflect the constitution of the respective populations. Women are not being studied in this protocol. The safety and immunogenicity of Gardasil in HIV-positive women is being studied in ACTG 5240, AMC-060 and ATN 064.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by AMC and ATN policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical supporter(s) prior to submission.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: SCHEDULE OF EVENTS

Evaluation	Screening/ Pre-Entry (- 45 days)	Entry (D1) Injection 1	24-48 Hr Post	Wk 8 (± 7 days) Injection 2	24-48 Hr Post	Wk 24 (± 10 days) Injection 3	24-48 Hr Post	Wk 28 (± 10 days) Primary Endpoint	Wk 52 (± 28 days)	Wk 78 (± 28 days)	Wk 104 (± 28 days)	Early Study Discont.
Documentation of HIV	X											
Medical history/Medication history	X											
Concomitant medications/treatment modifications		X		X		X		X	X	X	X	X
Nadir CD4+ cell count	X ¹											
Complete physical exam	X											
Clinical assessments		X		X ²		X ²		X	X	X	X	X
Smoking status/sexual questionnaire/risk perception and knowledge survey		X		X		X			X	X	X	X
Vaccine/distribute vaccine report card		X		X		X						
Collect vaccine report card				X		X		X				
Telephone follow-up			X		X		X					
CD4+/CD8+		X ¹						X				X
Plasma HIV-1 RNA		X ¹						X				X
CBC with differential	X							X				X
Liver function tests	X							X				X
BUN/creatinine	X							X				X
Anal cytology	X ¹							X	X	X	X	X
Swab for perianal HPV DNA PCR	X ³							X	X	X	X	X
Swab for anal HPV DNA PCR		X ³						X	X	X	X	X
Swab for penile/scrotal HPV PCR		X ³						X	X	X	X	X
Urine testing for GC/chlamydia		X ³						X	X	X	X	
High resolution anoscopy	X ⁴							X	X	X	X	X
Anal biopsies ⁵	X							X	X	X	X	X
Serum HPV antibody testing		X ³						X	X	X	X	X
Oral HPV PCR testing and exam		X ³						X	X	X	X	X
ACSR Biopsy Donation (Optional if patient consents) ⁵	X										X	
ACSR Blood donation (Optional if patient consents)	X										X	

¹ To be obtained within 90 days prior to study entry

² HRA and anal cytology are not required assessments at Week 8 and Week 24. Visual inspection of the penis, scrotum, and perianal area should be done at Week 8 and Week 24.

³ Collect the swab, serum HPV, and oral specimens after the subject is deemed eligible for enrollment onto the study (segment B) and prior to the vaccination on Day 1.

⁴ HRA to occur at pre-entry visit prior to enrolling into Segment B.

⁵ Anal biopsies (if lesion is suspected).

⁶ Anal biopsies for ACSR donation may be obtained with the subject's consent from suspected lesions. The tissue biopsy for ACSR donation must be separate from the diagnostic biopsy.

APPENDIX II: KARNOFSKY PERFORMANCE SCALE

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	Description	Grade	Description
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX III: MERCK GARDASIL® PRODUCT INFORMATION

www.gardasil.com

APPENDIX IV: PENILE/SCROTAL SCRAPING PROCEDURES

To collect penile and scrotal cells for HPV testing, the foreskin will be retracted if present and the penile (shaft, glans and corona) skin and scrotal skin will be gently abraded with 600 grit emery paper followed by swabbing with a Dacron swab moistened with sterile saline. The swab from the Digene Female Swab Specimen Collection Kit (Catalog #5123-1220, 1-800-426-8157) will be inserted into a tube containing 1 mL of Sample Transport Medium (Digene). The swab should be placed in the collection vial and the end snapped off at the pre-scored line. Then the cap should then be replaced securely.

Sample Labeling

Each sample should be labeled with the following information:

- **Nine (9) Digit Subject ID:** “072-XXX-XXX”
- **Date of Sample Collection**
- **Specimen Type:** "Penile/Scrotal Swab"
- **Specimen Purpose:** “HPV DNA PCR”

Please refer to [Appendix VI](#) for shipping instructions.

APPENDIX V: ANAL CYTOLOGY SAMPLING PROCEDURES

All anal cytology specimens will be examined at the local institution.

Procedure for obtaining an anal cytology:

The subject should undress from the waist down, and either bend over the exam table or lay on his side in the fetal position. The examiner should use one hand to spread the buttocks and expose the anoderm. A Dacron swab moistened in sterile saline will then be inserted as far as is comfortable into the anus, a minimum of 2-3 inches. If there is difficulty inserting the swab, the subject should also retract their buttocks. With pressure on the distal end of the swab rotate it gently and slowly in a circular fashion as it is withdrawn over 15 to 30 seconds. Do not retract the buttocks when the swab is close to the verge to ensure that it is sampled as well. Immediately immerse the swab in a liquid-cytology vial agitating vigorously over 10 to 15 seconds to disperse the cells and then discard the swab.

All cytological specimens should be processed and examined locally. If insufficient or inadequate cytology results are obtained, the cytology assessment should be repeated if possible. Cytological slides from subjects who enter the trial should be available for central review upon request.

After the first swab has been immersed in the liquid cytology vial, a second moistened Dacron swab will be inserted and sample collected for HPV DNA testing (same procedure described above). **Please see [Appendix VI](#) for processing and shipping of the second sample collected for HPV DNA.**

APPENDIX VI: HPV DNA PCR SPECIMEN COLLECTION AND SHIPPING

All HPV DNA PCR specimens (penile/scrotal, perianal, and anal) will be collected at the local institution and shipped to the Palefsky Laboratory.

High resolution anoscopy is performed at screening and weeks 28, 52, 78 and 104. Biopsies are obtained if a lesion is suspected. One of the study outcomes is any incident AIN or anal/perianal condyloma associated with HPV 16, 18, 6 or 11 DNA as determined by PCR analysis of the anal tissue biopsy. Biopsies are fixed in formalin and sent to the local pathology lab for interpretation. We are requesting that the cassettes containing the biopsy be sent to the Palefsky lab. After the procedures described below are performed, the Palefsky lab will ship the remaining specimens back to the pathology lab that sent them.

Specimens may be shipped to the Palefsky lab quarterly and will be returned to the pathology lab within 1 month.

Procedure for obtaining perianal HPV DNA PCR sample

The perianal skin will be gently scraped with 600 grit emery paper followed by swabbing with a Dacron swab moistened with sterile saline. The wetted swab will then be placed into a container of STM (Specimen Transport Medium, DIGENE, Gaithersburg MD). The swab should be placed in the collection vial and cut with sterile or single-use scissors to allow the swab to fit in the vial. Then the cap should then be replaced securely.

Procedure for obtaining intra-anal HPV DNA PCR sample:

The procedure described above (in [Appendix V](#)) for collection of anal cytology should be repeated using a second Digene Female Swab Specimen Collection Kit (Catalog #5123-1220, 1-800-426-8157). The swab will be inserted into a tube containing 1 mL of Sample Transport Medium (Digene). The swab should be placed in the collection vial and cut with sterile or single-use scissors to allow the swab to fit in the vial. The cap should then be replaced securely.

*Note: Specimens will be processed for HPV DNA PCR, **not** Digene HCII.*

Specimens obtained for HPV testing (perianal, anal, and penile) should be stored at -80 C until shipment. All specimens can be shipped in batches. Specimens should be shipped **quarterly** on **dry ice** to the laboratory. Specimens should be shipped on **Mondays and Tuesdays only**.

Sample Labeling

Samples must be labeled with the bar-coded labels provided. Each sample should be labeled with the following information:

- **Nine (9) Digit Subject ID:** “072-XXX-XXX”
- **Specimen Type:** “Penile/Scrotal Swab”, “Perianal Swab” or “Anal Swab” or “Anal biopsy”
- **Specimen Purpose:** “HPV DNA PCR”
- **Date of Sample Collection**

Preparation and disposition of thinsections of anal biopsy tissue

The following procedures will be performed at the Palefsky Laboratory. The procedures will be performed according to the laboratory's SOP. The histotechnologist will ensure that the microtome and work areas are clean and free of contaminants. All Thinsection microtomy for PCR will be performed at a time when all other routine work has been completed, so potential contaminations can be minimized. Prior to sectioning each block, a new blade will be installed in the microtome. The blade will only be positioned so that it is at the left margin of the block surface. Technicians sectioning study blocks will utilize “biologically clean” gloves while handling the blocks (new gloves for each block). First, the technologist will face the block by removing two 4-micron sections from the face of the block. These sections will be discarded. Using sterile plastic forceps, the next two 4-micron paraffin sections are collected and floated in a water bath for the preparation of 1 H&E slide (Slide 1, with 2 sections). The forceps are discarded and a new blade is inserted into the microtome. Nine more 4-micron sections are cut and using the clean, central part of the microtome discarded after placing the cut section in each tube. Each tube is then placed inside a plastic sleeve and sealed. Slides and tubes should be labeled with subject's allocation number.

Two additional 4-micron sections are cut and 2 sections each are placed on 1 slide (Slide 2, with 2 sections) for H&E staining. Both H&E slides (Slides 1 and 2) will have a histopathologic review by the central laboratory's pathologist.

The microtome is cleaned in preparation for the next block and the process above is repeated. The microtome blade is replaced with a new blade and adjusted for each new biopsy block and the same procedure is to be followed. A new pair of clean gloves and a new pair of clean, disposable forceps will be used for each block being sectioned. The “used” blade may be retained for cutting non-PCR blocks. The total number of sections to be cut from each block is 13. A total of 2 slides and 9 tubes:

Slides 1, 2 (H&E), with 2 sections each, stained.

Tubes 1, 2, 3, 4, 5, 6, 7, 8, 9 (HPV PCR Analysis), 1 section per tube.

HPV PCR will be performed to detect HPV vaccine types as well as non-vaccine types according to the Palefsky Laboratory SOP.

Shipping

Please note that the shipment of these samples requires certified training in IATA regulations. All shipping materials can be ordered from SAF-T-PAK at www.saftpak.com.

- 1) Please use the Saf-T-Pak STP 340 shipper (each tube must be sealed with tape or parafilm under 2011 IATA rules). Place securely fastened tubes in the clear biohazard bag with the absorbent strip. Seal bag.
- 2) Place clear biohazard bag into the white Tyvek bag and seal bag.
- 3) Place white Tyvek bag into inner box.
- 4) Place the inner box into the STP 340 insulated box and cover with dry ice.
- 5) Seal the box and place your FedEx airbill on the outside.
- 6) Ship to the address below. **AMC SITES:** Please use the AMC ODMC FedEx account number to ship all HPV DNA PCR samples: # [REDACTED]. **ATN SITES:** Please use your local Fed Ex

number to ship all HPV DNA PCR samples.

7) Shipping address:

Joel Palefsky Laboratory
c/o Maria Da Costa
University of California, San Francisco
513 Parnassus Ave., Room S-420
San Francisco, CA 94143
Tel: 415-476-8885

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING.** Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package. STP-340 will come pre-printed with: Biological Substance Category B Marking, Exempt Human/Animal Specimen Marking, UN3373 Marking, Orientation Arrows, Class 9 Label and UN1845 Dry Ice Marking

Record of Specimens

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimen shipments.

APPENDIX VII: HIGH RESOLUTION ANOSCOPY (HRA)

Procedure for performing HRA:

High resolution anoscopy should only be done **after** the anal cytology and HPV DNA PCR are collected. The patient should undress from the waist down and lay on his side on the exam table in the fetal position. A mixture of 2% lidocaine jelly and water-soluble lubricating jelly should be used as a lubricant. A compound pharmacist can make the 2% lidocaine jelly. A digital rectal exam should be performed noting any masses or areas of induration. The procedure for HRA is as follows:

1. Insert the plastic disposable anoscope, remove stylet, place a cotton swab wrapped in gauze soaked in 3% acetic acid into anus, remove the anoscope over the swab and leave in place for 1 to 2 minutes.
2. Remove the swab and re-insert the anoscope. Carefully examine the anal canal with a colposcope.
3. Re-apply acetic acid as necessary to ensure adequate detection of lesions.
4. If acetowhitening is noted, note vascular characteristics, if present.
5. Lugol's solution (iodine) may be used as desired to identify areas of AIN near the squamocolumnar junction.
6. Biopsy up to six of the most abnormal appearing areas.
7. Apply acetic acid to perianal area and examine carefully with colposcope.
8. If planning to biopsy an external lesion, infiltrate areas with 1% lidocaine with epinephrine using a 30-gauge needle, if possible.
9. Biopsy area if a lesion is suspected.
10. A genital exam should be performed to note the presence of condyloma
11. Subjects with signs or symptoms consistent proctitis or sexually transmitted infections other than HPV should be referred for appropriate diagnosis and treatment.

Biopsies will be processed and read locally at the institution.

The tissue block, along with a copy of the surgical pathology report should be available for central review upon request. If the block is not available, a representative H & E stained section and six **stained** slides should be submitted. All materials will be retained unless return is specifically requested. Tissue will be evaluated for histology as demonstrated by H & E staining.

All slides should be sent to the following address for central pathology review:

Teresa M. Darragh, MD
UCSF/Mt. Zion Medical Center
Dept. of Pathology, Box 1785
1600 Divisadero Street, Room B217
San Francisco, CA 94115
Tel: 415-353-7861
Fax: 415-353-7676

Slides from UCSF that are read by local pathologist Dr. Teresa Darragh will be reviewed by Dr. Mieke van Zante for central review.

When affixing the specimen label, do not wrap the label around the slide as any protrusion at the bottom will result in the slide not sitting flat on the microscope stage. In addition, do not cover the slide's accession number. In some cases, the label may need to be trimmed to allow the barcode and 9-digit portion of the label to be affixed at the top of the slide.)

Shipping Instructions

1. Place the labeled slides into a specimen container or a slide box if available. Place the container or slide box in bubble wrap or other adequate cushioning. Use sturdy outer packaging to prevent breakage.
2. Affix the FED-EX airbill on blank side of the shipper.
3. Mark "OTHER" in the airbill under "Packaging".
4. Under airbill section "special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED".
5. Enter FED-EX account #: XXXXXXXXXX
6. Place "From/To" information onto areas provided on the shipper. Specimens are accepted MONDAY through THURSDAY only. All specimens should be shipped by **FedEx 2-day service** to Dr. Darragh at the address listed above:
7. Make certain that shipper is visibly labeled "Exempt human specimen."
8. RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
9. Place the box in the FedEx pickup area at your site or call to request a package pickup.

Record of Specimens

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimens.

APPENDIX VIII: ORAL EXAMINATION/TESTING STORAGE AND SHIPMENT

Please visit the AMC ODMC web site (www.amcooperations.com) for complete instructions related to Oral Examination & Diagnosis procedures and Oral Specimen Collection procedures.

Storage for specimens:

- Digene vials to be placed at -80° C until shipping
Note: Specimens will be processed for HPV DNA PCR, not Digene HCII.

Storage for oral fluid samples:

Whole saliva

- Patient will have expectorated 5 ml into a sterile 30 ml conical tube
- The saliva should then be stored at -80°

Throatwash

- A swish/gargle with 10 ml of Scope mouthwash will be housed in a sterile wide mouth 50 ml conical tube
- Centrifuge to collect a cell pellet by centrifugation at 1200 g for 10 minutes
- Pour supernatant into a 30 ml tube
- Using a pipette, transfer the cell pellet to a Digene HCII DNA collection kit transport container
- Label tubes with identifiers and as throatwash pellet or throatwash supernatant
- Place supernatant tube at -80° C for storage and cell pellet at -80° C

Saliva and throatwash specimens obtained should be stored locally at -80° C and shipped to the laboratory in batches. Specimens should be shipped **quarterly** on **dry ice** to the laboratory along with the anal and penile/scrotal swabs (see [Appendix VI](#)).

Sample Labeling

Samples must be labeled with the bar-coded labels provided. Each sample should be labeled using a Sharpie pen the following information:

- **Nine (9) Digit Subject ID: “072-XXX-XXX”**
- **Date and time of sample collection**
- **Specimen Type:** “Saliva”, “Throatwash pellet”. “Throatwash supernatant
- **Specimen Purpose:** “HPV DNA PCR”

Specimen Shipping and Handling Instructions

Please note that the shipment of these samples requires certified training in IATA regulations. All shipping materials can be ordered from SAF-T-PAK at www.saftpak.com.

These samples will be shipped in the same box as the same box as the anal and penile/scrotal samples. See protocol in [Appendix VI](#).

Order form for Oral Specimen Collection Kits

1 kit per patient visit includes:

- One 50 ml conical tube containing 10 ml of Scope
- Two 30 ml self-standing conical tubes
 - 1 for the 5 ml of saliva
 - 1 for Scope supernatant after spin
- One screw cap tube containing 1 ml Specimen Transport medium (STM) for oral rinse cell pellet (Digene HCII DNA collection kit transport container)
- 2-3 strips emery paper in autoclave pouch
 - 1 strip each for penile/scrotal, peri-anal
 - 1 strip for demonstration on patient's arm of emery paper abrasion – baseline visit only
- 2 un-scored swabs
 - 1 for liquid anal cytology
 - 1 for HPV DNA
- Return FedEx Airbill – Please write in your site's FedEx account number

Kits can be ordered by emailing, calling or faxing an order request to the following (email is preferred):

Joel Palefsky Laboratory
c/o Maria Da Costa
University of California, San Francisco
513 Parnassus Ave., Room S-420
San Francisco, CA 94143
Tel: 415-476-8885
Fax: 415-476-9364
Email: maria.dacosta@ucsf.edu

AMC/ATN site requesting oral kits _____

of kits needed _____

Kits to be sent to: _____

Please include either a phone number or email address in your contact information for questions.

APPENDIX IX: SERUM HPV ANTIBODY TESTING

Blood/Serum Collection

- Collect at least 7 ml of blood for serum separation. After blood is drawn, invert collection tube 5 times and allow the blood to clot 30-60 minutes in the tube. All blood specimens should be collected in a red top collection tube (Not a serum-separator tube).
- Red-top tubes for serum collection are provided by the investigative site.
- Once clotted, the collection tube should not be allowed to sit at room temperature or refrigerated for more than 1 hour prior to centrifugation and separation of the serum from the clot.
- Centrifuge the collection tube for 10 minutes at 1100-1300 g.
- After separation, the serum should be aliquoted (1.5 mL for serum retention; remainder of serum for HPV serology testing) and frozen immediately.
- Sera must be stored at -20°C or below.

Serum Labels

- All serum labels are provided by Merck/PPD. Please submit all requests for additional labels with sufficient lead time (generally 15 business days).
- All sites will be provided with regular labels (per subject, per visit interval) and blank labels that can be used for any subject, any interval in the event of loss or damage to regular labels.
- Serum specimens must be labeled with the bar-coded labels provided. Each sample should be labeled using indelible ink (Sanford Sharpie Industrial Extra Fine Point Super Permanent Ink-Item #13801) with the following information:
 - **Nine (9) Digit Subject ID: “072-XXX-XXX”**
 - **Date of Sample Collection (in the universal format dd-mon-yyyy)**

Blank Labels will need:

- **Merck assigned BN (allocation number)**
- **Visit interval**
- Please use the following format for all documented dates: **DD/MMM/YYYY (01-JAN-2008)**.
- **IMPORTANT: Labels should be affixed to serum vial at the top of the vial when possible.**
- If bar-coded labels do not adhere to the serum vial for any reason, they should be affixed to the vial with a single strip of clear tape so that the bar-code is clear and legible.

Serum Storage

- All serum specimens should remain frozen at -20C until ready for shipment.
- If applicable, retention sera should be held frozen at the site until notification that they can be destroyed or until requested by Merck (PPD).

Serum Packing and Shipping Supplies

- Complete the Inventory List of Samples form (located at the end of this appendix). Ensure that you print a copy of the completed form detailing the contents of each shipment. This must accompany all sample shipments.

- The completed Inventory List of Samples form should be faxed to PPD at 215-652-5843 or 215-993-0706 prior to every shipment. A Fax Notification Cover Sheet (located at the end of this appendix) should also be completed and serves as the cover sheet for your fax.
- After filling the cell box with serum vials in order according to the inventory sheet, place the cell box inside one of the large plastic bags with absorbent material and seal the bag. (Repeat as necessary, up to two (2) cell boxes per container).
- Place the specimen bags (containing the cell boxes) at the **bottom** of the Styrofoam cooler (no dry ice should be placed directly underneath the specimens).
- Place the original Inventory List of Samples form in a plastic bag and place it on top of the cell boxes. (Please be sure to maintain a copy of the form on site.) **PPD cannot inventory the serum if they are not accompanied by a completed inventory form.**
- Use the cardboard spacer provided to cover the serum. (If needed, please fill the empty space in the box with cardboard or newspaper to stabilize the cell boxes during transit).
- Fill the remaining space in the box with a **minimum of 5 pounds (2.3 kilograms) of dry ice.** After loading the dry ice on top of the spacer, place the lid on the Styrofoam box, close the flaps of the outer cardboard box, and seal with clear shipping tape.
- Record the amount of dry ice on the UN1845 label. Affix the completed air bill.
- **AMC SITES:** Please use the AMC FedEx account number (#[REDACTED]) for shipment of all serum samples to Merck/PPD. **ATN SITES:** Please use your local FedEx account number for shipment of all serum samples to Merck/PPD.

Shipments to PPD

- Serum shipments to Merck (PPD) should be sent quarterly **on the first Monday or Tuesday of the month** (or as requested by the Clinical team) to the following address:

PPD, LLC Vaccine and Biologics
Letitia Holt/Louis Bussells
466 Devon Park Drive
Wayne, PA 19087 USA
Telephone: 610.989.5337
Fax: 610.989.8353
letitia.holt@ppdi.com

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. **(IATA Packing Instruction 650 is located on the AMC web site.)**
- A *Shipper's Declaration for Dangerous Goods* is **not** required. However, for all dry ice shipments, the following information must be shown in sequence on the airway bill in the "Nature and Quality of Goods" box: Dry Ice, 9, UN1845, number of boxes being shipped, net weight of dry ice per box.

PPD Vaccine and Biologics

TO: _____

PHONE: _____

Shipping questions-Letitia Holt (610.989.5337)

COMPANY: PPD Vaccine and Biologics
Sample Management
Letitia Holt/ Lou Bussells
466 Devon Park Drive
Wayne, PA 19087, USA
Country: _USA_____

FAX NUMBERS: 610-989-8352

DATE: _____

FROM (Investigator): _____

(Study site contact): _____

CLINIC: _____

SENDER COMPANY: _____

STREET ADDRESS: _____

CITY & STATE: _____

SENDER PHONE NUMBER: _____

SENDER FAX NUMBER: _____

TOTAL # OF PAGES TO FOLLOW: _____

NOTIFICATION OF SPECIMEN / SAMPLE SHIPMENTS:

PROJECT NAME/ "V" or "MK" NUMBER	
STUDY NUMBER (Protocol # - Site #)	
DATE SPECIMENS/SAMPLES SHIPPED	
NUMBER OF SPECIMENS/SAMPLES SHIPPED	
SAMPLE TYPE (required--i.e., Serum, Plasma, PBMC, Thin section, Swabs, etc)	
NUMBER OF INNER PACKAGES (e.g., CELL BOXES)	
NUMBER OF SHIPPING BOXES SENT	
NAME OF COURIER (e.g., Fed-Ex, DHL, World Courier, etc.)	
SHIPMENT AIBILL, TRACKING OR JOB NUMBER	

Inventory List of Samples Form

Inventory List of Samples (page ____ of ____)

INm

Compound V501	Merck Protocol	Protocol AMC-072
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Human Papillomavirus Vaccine

INVENTORY LIST OF SAMPLES									
Samples sent from:					Name of Carrier:				
Date Samples Sent:					Airway Bill Number:				
Shipment Prepared By:					Estimated Date of Arrival:				
Preparator's Telephone No.:					Fax No.:				
Number of Samples on this Page:					Number of Boxes:				
Total Number of Samples in Shipment:					Date Samples Received at Merck:				
AMC-072 SUBJ. ID	ALLOCATION NUMBER	STUDY INTERVAL (e.g., Day 1)	SAMPLE DATE (DD-Mon- YYYY)	SERUM	PENILE SWAB	SCROTAL SWAB	PERIANAL/ PERINEAL SWAB	RECTAL SWAB	COMMENTS
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

If this worksheet is used as a source document, it must be initialed and dated by the individual making the observation/recording.	Initials	DD-Mon-YYYY
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APPENDIX X: AMC DATA SAFETY MONITORING PLAN

(Version 5.0 • January. 28. 2014)

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (<http://ctep.cancer.gov/guidelines/index.html>). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC prior to submission to NCI and the sponsor. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met.

For phase III trials, the AMC has formed an independent Data Safety and Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the Statistician listed on the protocol, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The AMC Data Safety and Monitoring Board reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data Safety and Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the AMC DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site monitoring

visits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDCSM (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with a CTEP-AERS report, the AMC ODMC contacts sites to request an expedited report. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting via CTEP-AERS. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the AMC DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC site staff into AdvantageEDCSM. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts monitoring visits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a plan to correct deficiencies within 30 days. If needed, a repeat site visit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX XI: VACCINATION REPORT CARD

Study Site	Patient's/Subject ID 072- -	Visit
------------	---	-------

Protective effect of quadrivalent vaccine in young HIV-positive males who
have sex with males

A Multi-Center Trial of the AIDS Malignancy Clinical Trials Consortium and the Adolescent Trials Network

Vaccination Report Card

**Only the SUBJECT should complete this vaccination report card. Corrections to the
vaccination report card by the subject should be dated and initialed by the subject.**

The STUDY NURSE will enter the dates where needed.

Complete this card for **5 days after vaccination** (until ___/___/___)
and return the card to the study site when it is complete.

Subject's Comments:

Study Site Personnel Comments:

Study Site	Patient's/Subject ID 072- -	Visit
------------	---------------------------------------	-------

TEMPERATURE MEASUREMENT

It is very important that you take your temperature every day, starting on the day of vaccination through Day 5.

Take your temperature orally and record this temperature in the appropriate box below.

Take your temperature in the evening whenever possible. If you need to take your temperature more than once during the day, record the highest temperature taken that day.

TAKE ORAL TEMPERATURE EACH DAY.	DAY	DATE (month/day/year)	ORAL TEMPERATURE
	1		
	2		
	3		
	4		
	5		

NOTE: Day 1 temperature should be taken 4 hours after the vaccination. Afterwards, temperature is to be taken daily for 4 more days.

Date Completed: _____

Study Site	Patient's/Subject ID 072- -	Visit
------------	---------------------------------------	-------

INSTRUCTIONS FOR INJECTION SITE REACTIONS:

On the following pages entitled “Injection Site Reactions”, please measure any **swelling** or **redness** **AT THE INJECTION SITE**.

Estimate the **size** of the reaction at its largest from edge to edge. Use the ruler marks along the bottom of the page.

Mark the box that best describes the size of the reaction:

1 if the greatest width is anywhere in the area marked 1 (**Example A**)

2 if the greatest width is anywhere in the area marked 2

3 if the greatest width is anywhere in the area marked 3 (**Example B**)

Over 3 if the greatest width is in any area marked with a number over 3.

Write in the number. (**Example C**)

If the reaction is wider than the area marked 7, write 8.

On the following pages entitled “Injection Site Reactions”, please estimate the severity of any **pain** or **tenderness** or **other reactions** **AT THE INJECTION SITE**.

Mark the box that best describes the severity of the reaction using the following definitions:

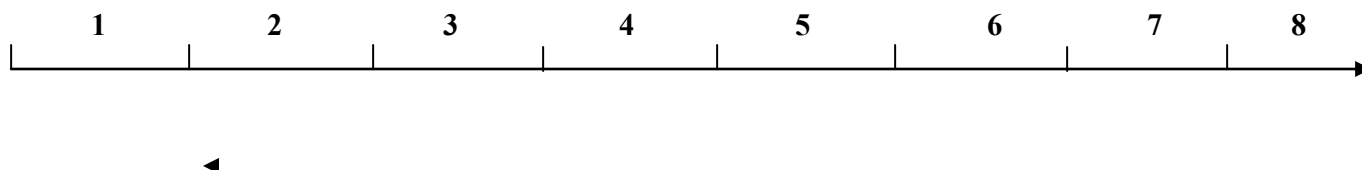
Mild is when you know it bothers you, but it doesn't bother you too much

Moderate is when it bothers you enough that you have difficulty doing your usual activities, like schoolwork or work

Severe is when it bothers you so much that you can't do your usual activities at all, like schoolwork or work

Complete one column each day, starting with Day 1 (the day of vaccination – 4 hours after injection). If the reaction continues past Day 5, please write in the last date it was present.

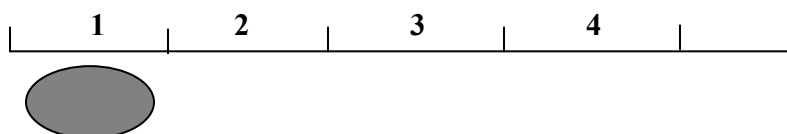
If an injection site reaction begins after Day 5, please estimate severity of the reaction in the box at the bottom of the pages entitled “Injection Site Reaction”.



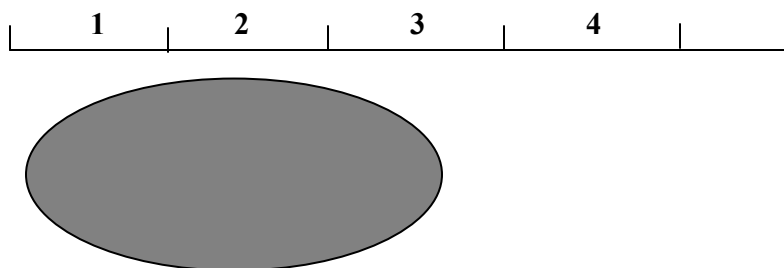
Study Site	Patient's/Subject ID 072- -	Visit
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EXAMPLES FOR MEASURING THE SIZE OF REACTIONS:

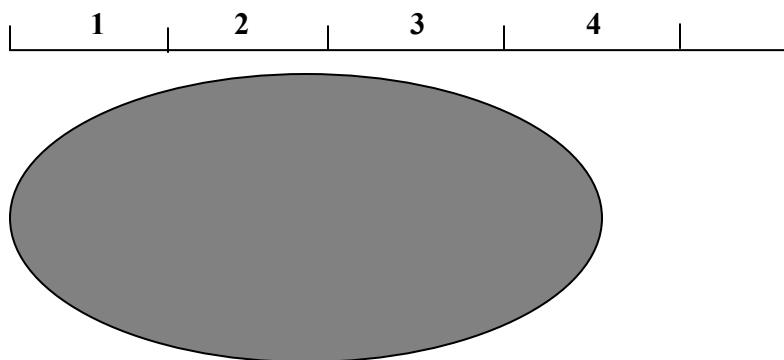
Example A: This reaction falls in the area marked 1 at its largest, so you would check the box marked “1”.



Example B: This reaction falls in the area marked 3 at its largest, so you would check the box marked “3”.



Example C: This reaction falls in the area marked 4 at its largest, so you would check the box marked “Over 3” and write in a 4.



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INJECTION SITE REACTIONS

Complete one copy of this page per injection site. Indicate the injection site for this page by checking the box below.

Injection Site (check one per page): ☐ Right Arm ☐ Left Arm Other _____

	DAY 1 Vaccination Day __/__/__ month/day/year	DAY 2 __/__/__ month/day/year	DAY 3 __/__/__ month/day/year	DAY 4 __/__/__ month/day/year	DAY 5 __/__/__ month/day/year	LAST DATE REACTION PRESENT __/__/__ month/day/year
SWELLING	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	__/__/__ month/day/year
REDNESS	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	__/__/__ month/day/year

PAIN OR TENDERNESS	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	__/__/__ month/day/year
OTHER INJECTION SITE REACTION (specify):	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	__/__/__ month/day/year
OTHER INJECTION SITE REACTION (specify):	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	<input type="checkbox"/> None <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> over 3: __	__/__/__ month/day/year

If an injection site reaction **began** 6 or more days after your vaccination, please record it below. Record the date it **started** and the **last date it was present**. Mark the box that best describes the severity of the injection site reaction.

INJECTION SITE REACTIONS BEGINNING 6 OR MORE DAYS AFTER VACCINATION	DATE (month/day/year)		SEVERITY
	Started	Last Present	
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe

1	2	3	4	5	6	7	8
---	---	---	---	---	---	---	---

Date Completed: _____

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OTHER COMPLAINTS OR ILLNESSES

Write down, in the boxes below, any other problems, complaints, or illnesses that either started or got worse during the 15 days after your shot.

Write down the date it started and the date it ended

Mark the box that best shows how much this complaint or illness bothered you, using one of the three words below:

Mild is when you know it bothers you, but it doesn't bother you too much

Moderate is when it bothers you enough that you have difficulty doing your usual activities, like schoolwork or work

Severe is when it bothers you so much that you can't do your usual activities at all, like schoolwork or work

Do not record injection site complaints on this page. Those complaints are recorded on the previous page in the table entitled "Injection Site Reactions".

List each complaint or illness separately.

If during the 15 days after vaccination you did not have any other complaints or illnesses check the box here: ☐ None

OTHER COMPLAINTS OR ILLNESSE	DATE (month/day/year)		SEVERITY
	Started	Last Present	
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe
			<input type="checkbox"/> mild <input type="checkbox"/> moderate <input type="checkbox"/> severe

Date Completed: _____

APPENDIX XII: SMOKING STATUS/RECENT SEXUAL HISTORY/RISK PERCEPTION AND KNOWLEDGE QUESTIONNAIRE

AMC-072 Smoking Status/Recent Sexual History

Patient ID number:

Date:

Study Week number:

NOTE TO STAFF: This questionnaire is to be administered following vaccination at protocol-specified time points. Please complete the three form fields above, and then give the questionnaire to the subject. The questionnaire must be self-administered and placed in an envelope and sealed after completion.

Thank you for taking this questionnaire. This form will ask about cigarette smoking. It will also ask about sex you may have had in the last 6 months.

- 1) How often do you currently smoke cigarettes? (Choose one)
☐ Not at all (skip to question #3)
☐ Some days
☐ Every day
☐ I prefer not to answer (skip to question #3)

- 2) On average over the past 6 months, how many cigarettes have you smoked per day? (1 pack equals 20 cigarettes)

The next few questions will ask about men you may have had sex with in the past 6 months. Let's review some words so that we agree on what we are talking about. By "having sex" we mean oral sex, anal sex or rimming.

ORAL SEX is when a man puts his penis in someone else's mouth or when a man has someone else's penis in his mouth.

ANAL SEX is when a man puts his penis into someone's rectum, anus, or butt (also known as insertive anal sex or being a top) or when a man has someone else's penis in his rectum, anus, or butt (also known as receptive anal sex or being a bottom).

RIMMING: When a man puts his mouth or tongue to someone's anus or butt, or someone else does that to him.

- 3) Have you ever had sex with a man (even only once)?
☐ Yes
☐ No (skip to question #12)
☐ I prefer not to answer (skip to question #12)

- 4) Have you ever had sex by having a penis inserted into your anus (even only once)?
___ Yes
___ No (skip to question #6)
___ I prefer not to answer (skip to question #6)
- 5) When was the last time you had sex by having a penis inserted into your anus?
___ Within the past week
___ Within the past month
___ Within the past six months
___ Within the past year
___ Over a year ago
- 6) Have you had sex of any kind with a man in the past 6 months?
___ Yes
___ No (Skip to question #12)
___ I prefer not to answer (Skip to question #12)
- 7) How many men have you had sex with in the past 6 months?
___ 1
___ 2 to 5
___ 6 to 10
___ more than 10
- 8) With how many men have you had receptive anal sex with in the past 6 months (i.e., have sex by putting their penis into your anus)?
___ 0 (Skip to question #10)
___ 1
___ 2 to 5
___ 6 to 10
___ more than 10
- 9) How often did your sex partner use a condom during receptive anal sex?
___ Every time (100%)
___ Mostly
___ Half the time
___ Occasionally
___ Never (0%)

10) How many men did you perform oral sex on during the past 6 months (i.e. have sex by putting your mouth on their penis)?

☐ 0 (skip to question #12)

☐ 1

☐ 2 to 5

☐ 6 to 10

☐ more than 10

11) How often did your sex partner use a condom during oral sex?

☐ Every time (100%)

☐ Mostly

☐ Half the time

☐ Occasionally

☐ Never (0%)

The next few questions will ask about any women that you have had sex with in the past 6 months. Let's start with reviewing some words so that we agree on what we are talking about. By "having sex" we mean vaginal sex, oral sex or anal sex.

ORAL SEX is when a man puts his penis in someone's mouth or when a man puts his mouth on a woman's vagina or clitoris.

VAGINAL SEX is when a man puts his penis in a woman's vagina.

ANAL SEX is when a man puts his penis into someone's rectum, anus, or butt.

12) Have you had sex with a woman in the past six months?

☐ Yes

☐ No (skip question #13 and #14)

☐ I prefer not to answer (skip question #13 and #14)

13) How many women have you had sex with in the past 6 months?

☐ 0

☐ 1

☐ 2 to 5

☐ 6 to 10

☐ more than 10

14) How many women did you perform oral sex on in the past 6 months (i.e., have sex by putting your mouth on her vagina or clitoris)?

- ☐ 0
☐ 1
☐ 2 to 5
☐ 6 to 10
☐ more than 10

The next set of questions asks how you feel after getting vaccinated against HPV. Please mark with an “X” or checkmark “✓” in one of the boxes to show how strongly you agree or disagree with the following statements (0=strongly disagree, 5=neither agree nor disagree, 10=strongly agree)

AFTER GETTING VACCINATED AGAINST HPV ...										
1. I am <i>less worried</i> about getting HPV.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE					STRONGLY AGREE			
2. I am still <i>just as concerned</i> about getting HPV.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE					STRONGLY AGREE			
3. I think getting HPV will be <i>less of</i> a problem.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE					STRONGLY AGREE			
4. I am <i>less worried</i> that one of my sex partners could get HPV from me.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY		NEITHER					STRONGLY			

AFTER GETTING VACCINATED AGAINST HPV ...										
DISAGREE				AGREE NOR DISAGREE			AGREE			
5. There is <i>less of a chance</i> that I will get HPV than there used to be.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE				NEITHER AGREE NOR DISAGREE			STRONGLY AGREE			
6. I am <i>less worried</i> about getting an STI or STD (sexually transmitted infection or disease) <i>other than HPV</i> .										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE				NEITHER AGREE NOR DISAGREE			STRONGLY AGREE			
7. I am still <i>just as concerned</i> about getting an STI or STD <i>other than HPV</i> .										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE				NEITHER AGREE NOR DISAGREE			STRONGLY AGREE			
8. I think getting an STI or STD <i>other than HPV</i> will be <i>less of a</i> problem.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE				NEITHER AGREE NOR DISAGREE			STRONGLY AGREE			
9. I am <i>less worried</i> that one of my sex partners could get an STI or STD <i>other than HPV</i> from me.										
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE				NEITHER AGREE NOR DISAGREE			STRONGLY AGREE			

AFTER GETTING VACCINATED AGAINST HPV ...

10. There is *less of a chance* that I will get an STI or STD *other than HPV* than there used to be.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE						STRONGLY AGREE		

11. I feel that condom use during sex is *less* necessary.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE						STRONGLY AGREE		

12. I feel it is still *just as important* to have as few sexual partners as possible.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE						STRONGLY AGREE		

13. I feel it is *not as important* to talk to my sex partners about safe sex.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE						STRONGLY AGREE		

14. I think it is still *just as important* to use a condom every time I have sex.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE		NEITHER AGREE NOR DISAGREE						STRONGLY AGREE		

AFTER GETTING VACCINATED AGAINST HPV ...

15. I will be *less worried* about having unprotected sex.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
STRONGLY DISAGREE			NEITHER AGREE NOR DISAGREE					STRONGLY AGREE		

The next 5 questions ask about your HPV knowledge. Please mark whether you think the answer is true, false, or if you don't know.

QUESTION	RESPONSE
16. If a man's sexual partners use condoms, he is completely protected against HPV.	<input type="checkbox"/> True <input type="checkbox"/> False <input type="checkbox"/> Don't know
17. A person may be infected with HPV and not know it.	<input type="checkbox"/> True <input type="checkbox"/> False <input type="checkbox"/> Don't know
18. HPV can be spread from person to person just by skin to skin genital contact.	<input type="checkbox"/> True <input type="checkbox"/> False <input type="checkbox"/> Don't know
19. Genital warts always go away permanently if a man gets the right treatment.	<input type="checkbox"/> True <input type="checkbox"/> False <input type="checkbox"/> Don't know
20. HPV can sometimes be cured with antibiotics.	<input type="checkbox"/> True <input type="checkbox"/> False <input type="checkbox"/> Don't know

Thank you for taking this questionnaire!!

APPENDIX XIII: ACSR INFORMED CONSENT FORM – AMC-072

**RESEARCH STUDY
AIDS AND CANCER SPECIMEN RESOURCE (ACSR)**

A. INTRODUCTION

You are being asked to donate specimens (tissues and/or blood) for research. Before you decide to be a part of this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent.

This consent form provides information about the research study, which has been explained, to you. Once you understand the study and the tests it requires, you will be asked to sign this form if you want to take part in the study. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study.

B. PURPOSE

The National Cancer Institute has set up a Biorepository for tissues and biological fluids from HIV-positive and HIV-negative individuals in order to have specimens available for scientists studying cancers and pre-cancers associated with HIV disease.

Biopsy Tissue and Blood Donation

Individuals who are having high resolution anoscopy (HRA) as part of this research study are being asked for permission to donate an additional anal tissue specimen to the Biorepository. If it turns out that your physician needs more of your tissue for additional studies, the Biorepository will release all of your tissue back to your doctor.

It is expected that the biopsy tissues may be evaluated for human papillomavirus (HPV) detection and typing, and potentially other research assays as additional science studies are developed. This may also involve genetic testing. These evaluations will not be done in real time and you will not receive the results of these tests.

In addition, you are being asked permission to donate some of your blood (up to 20 milliliters) to the Biorepository so that scientists can better understand factors that may affect your risk of developing human papillomavirus (HPV)-related anal pre-cancers or other diseases that may occur in HIV-positive men. These evaluations will not be done in real time and you will not receive the results of these tests.

We will also ask you if you will let any leftover tissue or blood that is not used during the study be donated to ACSR at the end of the study.

Donation of blood or biopsy specimens is not a requirement to participate in the study and you may withdraw your approval for the storage of these specimens at any time. You may also choose to donate blood but not tissue, or vice-versa.

C. PROCEDURES

You are being asked for consent to place additional tissue and a blood sample in the ACSR. If you agree to allow the ACSR to have some of your tissue and/or blood, the following procedures will occur:

- Procedure for tissue donation: At the time you are seen for high resolution anoscopy (HRA), a swab moistened with acetic acid (i.e. diluted vinegar) is placed in your anus. Vinegar helps pre-cancers and warts in the anus show up. The doctor or nurse then re-inserts the plastic speculum into your anus. A colposcope (a machine similar to a magnifying glass) is used to see the skin inside the anus. Then biopsies of any areas worrisome for pre-cancer or anal warts may be performed. To do a biopsy, a small bit of skin about the size of a sesame seed is cut off. Iodine may also be used to help make pre-cancers show up, and an injection of lidocaine may be given to numb the skin before a biopsy.
- Procedure for blood donation: Two tubes (up to 20 milliliters) of blood will be drawn.

If you agree to make a tissue and/or blood donation to the ACSR, we would also like to confidentially obtain some clinical information from your medical records that could be useful to research investigators. The report of the information retrieved from your medical record that is given to research investigators will not have your name, or include any information which could personally identify you.

It is possible that you may not qualify for the study, based on the results of your screening visit. If you agree to donate tissue and/or blood, but do not qualify for the study, we would still be interested in sending the specimens to the Biorepository.

You will be asked if you are willing to make a tissue and/or blood donation to the ACSR at two time points: at the first visit and again about 2 years later. You may agree to donate specimens at either or both visits.

D. POSSIBLE RISKS

Some anal bleeding occurs with every biopsy. Serious bleeding is rare, about 1 in 1000 biopsies. If serious bleeding occurs, a simple procedure may be necessary to stop the bleeding such as burning or cauterizing the area. An injection of lidocaine may be given prior to a biopsy. It is possible that you can experience pain or dizziness from the injection. Rarely, you can experience an allergic reaction such as itching or swelling. Iodine may be used to help identify pre-cancerous areas of the anus. It is possible that you may have an allergic reaction.

There is a possibility of a bruise and slight pain at the time the blood samples are taken. There is also the possibility of fainting and infection at the site of the blood draw.

Risks of genetic testing include the possibility that the information will not remain private or confidential. All personnel who will have access to genetic information about you are ethically and legally obligated to maintain the confidence of that information. However, there can be no absolute guarantees. In rare cases where information has not remained private, this has caused problems for persons related to their employment and/or their life and/or health

insurance and other benefits or entitlements.

E. POSSIBLE BENEFITS

It may be that there will be no direct benefit to you by consenting to allow the ACSR to have your tissue and blood. However, there may be possible benefits to medical knowledge and HIV-infected individuals in the future.

F. COSTS

There will not be any additional costs to you for consenting to participate in the AIDS and Cancer Specimen Resource.

G. PAYMENT FOR INJURY OR HARM

As the lists of risks shows, taking part in this research study may result in injury or harm to you. If you require immediate medical care, you should go to an emergency room. Otherwise, the doctor in charge of the study will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. No funds have been set aside to compensate you in the event of injury. However, you are not giving up your right to seek to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

[ATN SITES: PLEASE USE THE FOLLOWING LANGUAGE:]

If you are injured as a result of being in this research study, you will receive immediate, short-term treatment as determined by [*name of hospital*] for the injury. The cost of the treatment will be charged to you or your insurance company, as would normally be done for your medical care. You will then be told where you could receive additional treatment for injuries. Your insurance carrier may or may not pay for treatments for injuries that are caused by taking part in this study. No monetary compensation (payment to you) or other forms of compensation for such injuries will be provided by the hospital or sponsoring agency.

H. PRIVACY

Your hospital medical records will be confidentially reviewed to obtain clinical information that could be useful to research investigators. However, the report of this information will not have your name or social security number anywhere on the report, so you will not be easily identified. The results of this research study will be given to the sponsor, the National Cancer Institute (NCI), AIDS Malignancy Consortium, and may be asked for by the Department of Health and Human Services, FDA and Pharmaceutical Collaborator. In addition, the Institutional Review Board may see your records. Except for these people, records from this study will be kept private unless you authorize their release or release is required by law (i.e. court subpoena). Any publications of this study will not use your name, identify you personally, or include any information that could personally identify you.

I. QUESTIONS

If you have any questions about this research study, you should contact Dr. (_____)

at *(Phone Number)* (day) or *(Phone Number)* (night), or the person in charge of the study, *()*, the study coordinator, at *(Phone Number)*. If you have any questions about your rights as a research subject, you should call *(IRB Representative)*, in *(Institution)* Office of Human Research at *()*. *(IRB Representative)* is your representative and is not employed by the individuals conducting the study.

J. OPTIONAL DONATIONS

- ☐ **Yes**, I agree to have an additional anal biopsy to donate for future research. I understand that I may not qualify for the research study based on the results of my screening visit and that this specimen will still be sent to ACSR.
- ☐ **No**, I do not want to have an additional biopsy to donate for future research.
- ☐ **Yes**, I agree to donate an additional blood specimen for future research. I understand that I may not qualify for the research study based on the results of my screening visit and that this specimen will still be sent to ACSR.
- ☐ **No**, I do not want to donate an additional blood specimen for future research.

K. SIGNATURES

Statement of professional obtaining consent

I have fully explained this research study to the subject or guardian of subject. In my judgment and the subject's or guardian's, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____ Physician's Signature: _____

Physician's Name: _____ (Print)

Patient's/subject (or guardian's) statement

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my/the subject's participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want (the patient/subject) to take part in it.

Date: _____ Patient/Subject (or guardian's) Signature: _____

Patient's/Subject's Name: _____
(Print)

Patient

Date

Person obtaining consent

Date

Witness

Date

L. LEFTOVER STUDY SPECIMENS

If you agree, excess blood, oral specimens and anal swab specimens may be donated to the ACSR and made available for research by other investigators. Storage of leftover specimens will not require additional procedures than those already taking place in the research study. Storage of leftover specimens is not a requirement to participate in the study and you may withdraw your approval for the storage of your leftover specimens at any time. These specimens may be held for an indefinite length of time. You will not be told of the results of the research done on these samples.

Please check one of the following boxes to indicate whether or not you wish to have your leftover specimens stored for AIDS-related research in the future.

☐ **Yes**, I agree to have my leftover specimens stored for future research.

☐ **No**, I do not want to have my leftover specimens stored for future research.

APPENDIX XIV: ACSR ASSENT FORM – AMC 072**RESEARCH STUDY
AIDS AND CANCER SPECIMEN RESOURCE (ACSR)****A. INTRODUCTION**

You are being asked to donate specimens (tissues and/or blood) for research. Before you decide to be a part of this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent.

This consent form provides information about the research study, which has been explained, to you. Once you understand the study and the tests it requires, you will be asked to sign this form if you want to take part in the study. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study.

B. PURPOSE

The National Cancer Institute has set up a place where tissues and blood are kept so that these specimens can be available for scientists studying cancers and pre-cancers associated with HIV disease in the future. This place is called the AIDS and Cancer Specimen Resource Biorepository (ACSR).

Biopsy Tissue and Blood Donation

You are having high resolution anoscopy (HRA) as part of this research study that involves taking an anal biopsy. Individuals in the study are being asked for permission to donate an additional anal tissue specimen to the Biorepository described above. In addition, you are also being asked permission to donate some of your blood to the Biorepository. We will also ask you if you will let any leftover tissue or blood that is not used during the study be donated to ACSR at the end of the study.

Any tissue and blood collected may be tested for types of human papillomavirus (HPV) and other research tests might be performed so that scientists can better understand HPV-related anal pre-cancers and other diseases that may occur in HIV-positive men. These future tests may also involve genetic testing. These tests will not be done now, so you will not receive the results of these future tests.

Donating tissue or blood specimens is not a requirement to participate in the study and you may withdraw your approval to store these specimens at any time. You may also choose to donate blood but not tissue, or vice-versa.

C. PROCEDURES

You are being asked to place additional tissue and a blood sample in the Biorepository. If you agree, the following procedures will occur:

- Procedure for tissue donation: At the time you are seen for high resolution anoscopy (HRA), a swab moistened with acetic acid (i.e. diluted vinegar) is placed in your

anus. Vinegar helps pre-cancers and warts in the anus show up. The doctor or nurse then re-inserts the plastic speculum into your anus. A colposcope (a machine similar to a magnifying glass) is used to see the skin inside the anus. Then biopsies of any areas worrisome for pre-cancer or anal warts may be performed. To do a biopsy, a small bit of skin about the size of a sesame seed is cut off. Iodine may also be used to help make pre-cancers show up, and an injection of lidocaine may be given to numb the skin before a biopsy.

- Procedure for blood donation: Two tubes (up to 2 tablespoons) of blood will be drawn.

If you agree to make a tissue and/or blood donation to the Biorepository, we would also like to confidentially obtain some clinical information from your medical records that could be useful to research investigators. This report that is given to research doctors will be coded, that means it will not have your name, or include any information which could personally identify you.

It is possible that you may not qualify for the study, based on the results of your screening visit. If you agree to donate tissue and/or blood, but do not qualify for the study, we would still be interested in sending the specimens to the Biorepository.

You will be asked if you are willing to make a tissue and/or blood donation at two different times: at the first visit and again about 2 years later. You may agree to donate specimens at either or both visits.

D. POSSIBLE RISKS

Some anal bleeding occurs with every biopsy and there is a risk of infection. An injection of lidocaine may be given prior to a biopsy to numb the area and it is possible that you can experience pain or dizziness from the injection, or an allergic reaction. Iodine may be used to help identify pre-cancerous areas of the anus and it is possible that you may have an allergic reaction to iodine.

There is a possibility of a bruise and slight pain at the time the blood samples are taken. There is also the possibility of fainting and infection at the site of the blood draw.

Risks of genetic testing include the possibility that the information will not remain private or confidential, even though people who have this information are legally required to keep the information private. If this information were released, there is a chance problems will occur in your job, or with your health insurance, or other benefits you might have. It is unlikely that this information would be released, but there can be no absolute guarantees.

E. POSSIBLE BENEFITS

There may be no direct benefit to you by consenting to allow the ACSR Biorepository to have your tissue and blood. However, there may be possible benefits to medical knowledge and HIV-infected individuals in the future.

F. COSTS

There will not be any additional costs to you for agreeing to participate in donating tissue or blood to the Biorepository.

G. PAYMENT FOR INJURY OR HARM

It is important that you tell your study doctor, if you feel that you have been hurt because of taking part in this study. As the lists of risks shows, taking part in this research study may result in injury or harm to you. You will be sent a bill for whatever medical care you receive. No funds have been set aside to compensate you in the event of injury. However, you are not giving up your right to seek to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

[ATN SITES: PLEASE USE THE FOLLOWING LANGUAGE:]

If you are injured as a result of being in this research study, you will receive immediate, short-term treatment as determined by [*name of hospital*] for the injury. The cost of the treatment will be charged to you or your insurance company, as would normally be done for your medical care. You will then be told where you could receive additional treatment for injuries. Your insurance carrier may or may not pay for treatments for injuries that are caused by taking part in this study. No monetary compensation (payment to you) or other forms of compensation for such injuries will be provided by the hospital or sponsoring agency.

H. PRIVACY

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

I. QUESTIONS

If you have any questions about this research study, you should contact Dr. (_____) at (*Phone Number*) (day) or (*Phone Number*) (night), or the person in charge of the study, (_____), the study coordinator, at (*Phone Number*). If you have any questions about your rights as a research subject, you should call (*IRB Representative*), in (*Institution*) Office of Human Research at (_____. (*IRB Representative*) is your representative and is not employed by the individuals conducting the study.

J. OPTIONAL DONATIONS

☐ **Yes**, I agree to have an additional anal biopsy to donate for future research. I understand that I may not qualify for the research study based on the results of my screening visit and that this specimen will still be sent to ACSR.

☐ **No**, I do not want to have an additional biopsy to donate for future research.

- ☐ **Yes**, I agree to donate an additional blood specimen for future research. I understand that I may not qualify for the research study based on the results of my screening visit and that this specimen will still be sent to ACSR.
- ☐ **No**, I do not want to donate an additional blood specimen for future research.

K. SIGNATURES FOR ASSENT

You have been given copies of this assent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date Participant's Signature for Assent

Date Person Obtaining Assent

Statement of professional obtaining assent

I have fully explained this research study to the subject or guardian of subject. In my judgment and the subject's or guardian's, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____ Physician's Signature: _____

Physician's Name: _____ (Print)

L. LEFTOVER STUDY SPECIMENS

If you agree, excess blood, oral specimens and anal swab specimens taken during the study may be donated to the ACSR and made available for research by other investigators. Storage of leftover specimens will not require additional procedures than those already taking place in the research study. This is not a requirement to participate in the study and you may withdraw your approval for the storage of your leftover specimens at any time. These specimens may be held for an indefinite length of time. You will not be told of the results of the research done on these samples.

Please check one of the following boxes to indicate whether or not you wish to have your leftover specimens stored for AIDS-related research in the future.

- ☐ **Yes**, I agree to have my leftover specimens stored for future research.
- ☐ No, I do not want to have my leftover specimens stored for future research

APPENDIX XV: AIDS AND CANCER SPECIMEN RESOURCE (ACSR) – SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

A. GENERAL

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: SPECIMENS MUST BE SHIPPED MONDAYS THROUGH WEDNESDAY AS AN OVERNIGHT PRIORITY SHIPMENT. SPECIMENS ARE NOT ACCEPTED ON FRIDAYS, SATURDAYS, OR SUNDAYS IN THE ACSR.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

BLOOD SPECIMENS

Draw two 8.5 cc (ml) yellow top [acid citrate dextrose (ACD) Solution A] tubes from study patient. With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol #072
- AMC Subject ID#
- Date and time of collection
- Specimen type, i.e., S=Serum, or Tissue
- Specimen purpose: Donation

Specimen Shipment

- Seal the tops of the two 8.5 cc yellow tops with parafilm.
- Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and “self-seal”.
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Affix the FED-EX airbill on blank side of the shipper making sure that it is marked “FED-EX PRIORITY OVERNIGHT”.
- Mark “OTHER” in the airbill under “Packaging”. **AMC SITES:** Please use FedEx Account # [REDACTED]. **ATN SITES:** Please use your local FedEx account number for shipment of all ACSR samples.
- Under airbill section “Special Handling” indicate “YES-SHIPPERS DECLARATION NOT REQUIRED”.
- Place “From/To” information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

**Dr. Sylvia Silver/Bank Technologist
George Washington University Medical Center
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-3422
Fax: (202) 994-5056**

- Make certain that shipper is already either pre-labeled with 'UN#3373' stamp, or make a paper label with 'UN#3373' and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in ml and affix to the shipper.
- Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON FRIDAY

Preparation of Plasma and Mononuclear Cells

It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Materials

- Lymphocyte Separation Medium (LSM Solution, Ficoll-Hypaque - sterile)
- 15 ml conical centrifuge tubes (sterile)
- PBS (sterile)
- 1, 5 ml and 10 ml serologic pipettes (sterile)
- NUNC tubes
- Alcohol-saturated, control rate freezer container
- DMSO freezing media:
- 50% Cryoprotective Medium, Cambrex (catalog no.:12-132A)
- 50% Heat Inactivated Fetal Bovine Serum

Preparation of Plasma Samples

- The 8.5 ml tubes of whole blood in ACD should be rotated gently two or three times before being centrifuged. Do not transfer before centrifugation.
- The cells are separated by centrifugation at 500 g for 10 minutes.
- 0.5 ml aliquots of plasma are removed and put into separate 1.5 ml screw top tubes (NUNC) and transferred to liquid nitrogen storage.

PERIPHERAL BLOOD MONONUCLEAR CELL (PBMC) SEPARATION AND FREEZING

- The cells and plasma remaining from the previous step are transferred into a 15 ml conical tube or 50 ml centrifuge tube depending on volume.
- Sterile PBS should be added to the suspended cells whole blood cells in an equal volume and pipetted up and down to mix (1:1).
- The whole blood-PBS mixture should be carefully overlaid onto 4-5 ml of room temperature LSM or Ficoll-Hypaque solution in a sterile 15 ml conical centrifuge tube. A sharp interface should exist between the LSM and the whole blood mixture. (If the layer of LSM gets mixed with the blood-PBS, the tube should be gently rotated to mix the blood, PBS, and LSM, and transfer to a 50 ml sterile conical tube. An equal volume of PBS is added, and the cells are separated at 600 g for 15 minutes. After removal of LSM-PBS supernatant, return to Step b).
- Centrifuge the 15 ml conical tube for 30 minutes at 900 g at room temperature. The mononuclear leukocytes (principally lymphocytes and monocytes) will band at plasma/LSM interface.
- The fluffy white layer just below the plasma layer should be aspirated off and transferred to an appropriately labeled 15 ml sterile conical centrifuge tube. Be careful to remove only the interface and a minimum amount of the LSM or Ficoll-Hypaque.
- Add three volumes of PBS to the cell suspension and or enough to fill conical and mix by pipetting up and down.
- Centrifuge at 500 g for 10 minutes.
- Aspirate off and discard supernatant, taking care not to disturb pellet.
- Resuspend in 12 ml of PBS. Take 10 μ l of suspension for cell counting (dilute accordingly whether using a hemocytometer or automated cell counter). Centrifuge again for 10 minutes at 500g to wash cells.
- Using a 1 ml pipette, the *DMSO freezing mixture should be added dropwise to the cell pellet suspension. Gently finger-tap between drops to resuspend cells. If the cell pellet is small, only 0.5 ml of freezing media is added (and only one aliquot of cells is frozen). If the cell pellet is large, up to-2 ml of freezing media can be added in a drop wise fashion. (Cell densities of 1 - 10 million PBMC/ml are best for cryopreservation. If a hemocytometer is available, the optimal concentration is 5×10^6 PBMC/ml).

***Important: Do not put the DMSO containing media on the cell button all at once.**

- Freeze the cell suspension in 0.5 ml aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.**

PREPARATION OF TISSUE SAMPLES

Tissue specimens to be fresh frozen should be placed in OCT and then on dry ice

immediately. The specimens may stay on dry ice until being transferred to a -80°C freezer.

Tissue specimens for donation may be batched for shipping after storage in -80°C freezer.
*NOTE: Specimens can only be accepted **Monday** through **Thursday**. Therefore, specimens can only be shipped **Sunday-Wednesday** for delivery the next day. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Dr. Sylvia Silver/Bank Technologist
George Washington University Medical Center
2300 I Street, NW
Washington, DC 20037
Phone: (202) 994-3422
Fax: (202) 994-5056

C. RECORD OF SPECIMENS

This study will track specimens via GlobalTraceSM, a component of the AMC AdvantageEDCSM system. The GlobalTraceSM shipment manifest must accompany all specimen shipments.